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The Science of Biomimetics: Imitating Nature for Almost Natural Solutions

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ABSTRACT

Biomimetics is a scientific discipline that explores the elegant designs found in nature. It has been effectively applied in renowned projects such as the Eiffel Tower, which was inspired by the trabecular structure of bone. In dentistry, the use of biomimetic concepts and protocols aims to preserve tooth structure and vitality, extend the lifespan of dental restorations, and prevent future retreatments. Biomimetic dental materials are naturally biocompatible and possess excellent physical and chemical properties. They have been successfully utilized in various dental fields, providing benefits such as increased strength, sealing, regenerative ability, and antibacterial properties. Many biomimetic materials have also overcome significant limitations of earlier generations of materials. Therefore, this review article aims to shed light on recent developments in the emerging field of biomimetics, specifically in restorative and regenerative dentistry. The review covers different approaches to restoring, remineralizing, and regenerating teeth, as well as various biomimetic dental restorative and tissue engineering materials.

Keywords: *Biomimetic dentistry, Biomimetic materials, Glass ionomer cement, Ceramics, Composite resin, Regenerative endodontics, Calcium hydroxide, MTA, Biodentine, Bioceramics, Triple antibiotic paste.*

1. INTRODUCTION

The term biomimetic comes from the Latin word bios(life), and mimesis, meaning imitation or mimic [1]. Biomimetics is an interdisciplinary field that involves replicating nature's optimal biological approaches and strategies using concepts from chemistry, physics, mathematics, and engineering to create innovative synthetic materials and organs [2]. Some famous examples of biomimetics include swimwear that mimics the dermis in shark skin, needles inspired by mosquitoes, and wind turbine blades shaped like whale fins [3].

The term "biomimetic" was first coined by American inventor Otto Schmitt in 1950. In 1960, the concept of imitating, copying, and studying biology was coined "bionics" by Jack Steele [3,4]. The term biomimetic was first officially listed in Webster's dictionary in 1974.

Bio-mimetic dentistry uses enamel, dentin, bone, cementum, etc. to repair damaged teeth. involves the use of restorations that replicate the appearance, function, and strength of living tissue [5].

The secondary aim of biomimetics is to create materials that can restore the natural tooth's biomechanics. Biomimetics has been extensively studied at the molecular level for its potential to promote wound healing and regeneration of both soft and hard tissues [6].

2. BIOMIMETIC RESTORATIVE DENTISTRY

The goal is to restore the full functionality of hard tissues (enamel, dentin, cementum) using restorative materials that can reproduce or restore the biomechanics of natural teeth. This allows the teeth to function as a cohesive unit against functional forces and provide normal aesthetics and biology [2].

i. A typical extension to the preventive approach is:

Traditional dental restoration plans involve removing diseased and healthy tooth structure and replacing it with a solid, non-reactive material. However, this approach usually weakens the remaining tooth structure and results in short-term restorations [7].

ii. Biomimetic approach:

The idea of "less or no dentistry" has gained popularity in recent years as a conservative approach to restoring teeth and simulating natural teeth. Biomimetic recovery protocols aim to achieve this goal by reducing stress and increasing connection. Cavities and other lesion are carefully treated with advanced materials and adhesives to preserve the natural features of the teeth [7].

As improved adhesive and immediate dentin sealing developed, the use and indications for the core material decreased. Traditionally, this material has several functions, including a partial layer for biological protection in the deep preparation area, a general layer for dentin isolation from chemical or thermal injury, and dentin replacement before restorative procedures. Currently, the main indication for underlaying under an adhesive restoration is to keep the pulp in the form of a partial layer using Ca (OH_2) cement. Modern adhesives can now replace their former functions varnish and cement. The core material is mainly used to reduce the volume of the entrance / cover (e.g. excessive depth) and even make the geometry of the preparation sufficient to provide the cavity floor and fill the internal costs.

3. BIOMIMETIC RESTORATIVE MATERIALS

a. Glass ionomer (man-made dentin):

Glass ionomer cement (GIC) has been used as a restorative material in dentistry since the 1970s. They have attractive properties for clinical use, including good adhesion to tooth structure, fluoride release, and biocompatibility. However, it has some weaknesses, such as low power in the initial phase of the reaction, short working time, roughness, and sensitivity to moisture contamination. To overcome these limitations, the structure of the GIC has been modified.

GIC-HA hybrid is one of the modifications produced by the addition of nano-hydroxyapatite (HA) particles to GIC. This hybrid improves mechanical properties, antibacterial efficacy and fluoride release [8]. Garoushi et al. [9] made another modification where he added Solid and hollow discontinuous glass fiber fillers to the GICs, which increase fracture toughness and flexural strength. In addition, plant extracts such as *Olea europaea*, *Salvadora persica* and *Ficus carcia* (by Singer et al. 2020) [10] are added to GIC to increase its antimicrobial activity against bacteria such as *S. mutans* and *M. luteus*. increase compressive strength at high concentration. These changes make GIC a promising material for various dental applications, including man-made dentin.

b. Dental Composite Resin:

Hybrid organic and hybrid inorganic composites being organic and inorganic components are found in various natural structures such as teeth, shells, corals, and bones [11]. The performance and characteristics of these hybrids are influenced by the composition of each component. Dental composite resin (DCR) is an important category of hybrid biomaterials consisting of a resin matrix and an inorganic filler [12]. DCR has been widely used in dentistry since the 1960s to restore diseased and defective teeth due to its excellent aesthetics, biocompatibility, and ease of use [13].

The resin system composite is a self-healing/bleeding material that uses a biomimetic strategy to achieve a self-healing function. Some materials, such as bone, are self-healing composites that have the ability to heal even with significant fractures. Self-healing can be either internal or external, where compensatory molecules are produced only in response to damage, or when the material has been stored (extrinsically) [14].

An extrinsic energy source to drive reactive behaviour is required for Intrinsic self-healing which occurs at molecular level [15]. Self-healing materials, on the other hand, use polymer capsules that burst near the defect to release the resin that reacts with the existing catalyst to heal the crack. These materials can be visually enhanced by adding highly visible dyes, such as fluorescent dyes, to show damage [16,17]. Duo-layered resin composite is a novel biomimetic restorative system that mimics the structure of fibrous dentino-enamel complex [18]. The structure includes a basal layer made of fiberglass-reinforced composite resin (FRC) and a more polished and wear-resistant resin compound. The FRC base in the filler composite functions as a crack propagation barrier layer for the restoration [19].

c. Ceramics:

The natural appearance of teeth can be enhanced with dental ceramics, which have become more popular over the past 30 years with the development of computer-based dental technology and the concept of "digital workflow" in dentistry [20]. Researchers have long sought to produce dental biomimetic restoration ceramics. In 2000, Holland et al. The development of apatite-leucite glass ceramic containing building blocks of needle-point apatite similar to those found in living dental tissue. These needle-point crystals improve the aesthetic and mechanical properties of the material [21-23].

Biomimetic dental ceramics should provide gap-free adhesion to the restored tooth substance and promote the natural regeneration of the surrounding tissue. Goudouri et al. [24] results in adding apatite-forming capabilities to commercial dental restorative ceramic materials to improve tissue bonding, with examples showing an apatite-like layer formed on the surface without affecting the material's flexural strength. Biomimetic applications of dental ceramics include bioactive coated ceramic implants. Various commercially available bioactive glass-ceramics have been used to coat titanium and zirconia dental implants, resulting in improved osseointegration and tissue bonding [25].

Hybrid ceramics are another example of biomimetic ceramic materials that aim to combine the advantages of ceramics and composites to achieve physical properties similar to enamel and dentin, such as Young's modulus and strength [26]. Polymer-intercalated ceramic mesh (PICN) material consists of porous ceramic mesh (75-80% of the thickness) impregnated with polymer to mimic the structure of natural teeth [27].

Recently, materials science researchers have developed functionally graded PICNs characterized by compositional and structural gradients to produce structures with enamel and dental properties [1].

Making artificial and dentin-like materials with different physical and optical properties is a challenge due to the complex structure of teeth. However, recent advances in dental ceramics have allowed manufacturers to incorporate gradient shades and clarity into their products. The biomimetic concept has been extended to amplify gradients in single ceramic blocks. A new type of multi-layered zirconia block combining different types of zirconia has been developed to achieve high mechanical stability and desired aesthetics. This monolithic restoration consists of partially stabilized tetragonal zirconia polycrystal (3Y-TZP) in the occlusal area and 5Y-TZP in the occlusal area [28].

4. BIOMIMETIC REGENERATIVE DENTISTRY

Biomimetic dentin remineralization material

Bioactive ingredients

1. Bioactive glass (BAG) :

The first bioactive glass (BAG) was developed by Hench in 1969 [29]. Due to its ability to extract ions to form apatite crystals that resemble natural apatite in hard tissue, BAG has shown excellent regenerative potential for hard tissue repair. BAG has a unique composition of common components of human tissue, such as sodium, calcium, phosphorus, and silica, making it a bioactive material for several medical purposes. In dentistry, BAG is used for tissue engineering with titanium and ceramic implants to promote bone regeneration [30].

When BAG comes into contact with water or saliva, it releases calcium, sodium, and phosphorus ions that promote remineralization in tooth tissue. In addition, calcium phosphate deposits clog the tubule and prevent the movement of dental fluid, which is sensitive to the sensitivity of the teeth, according to the hydrodynamic theory [31]. Because BAG is not cytotoxic, it can also be used in pulp capping procedures and has been reported to promote reparative dentin formation [30].

2. Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) :

The bioactive complex CPP-ACP is a combination of casein phosphopeptide (CPP), which is derived from the casein protein found in milk, and amorphous calcium phosphate (ACP), which is a precursor for the formation of hydroxyapatite in the body. Its potential to prevent enamel demineralization and promote enamel and dentin remineralization has been demonstrated in toothpastes, sugarless gums, mouthwashes, and dental biomaterials such as composite resins and glass ionomers [32-34].

The CPP-ACP complex stabilizes calcium and phosphorus ions in the form of ACP, preventing spontaneous crystallization.

Nano aggregates also help localize calcium, phosphate and hydroxide ions on the tooth surface and maintain a supersaturated state in the plaque fluid [35]. If the pH drops to 5.8 or below, hydroxyapatite precipitates and diffuses into the subsurface to promote enamel remineralization at the lesion site. Combining CPP-ACP with fluoride has been found to increase the remineralization effect of porous and erosive lesions [36].

3. Fluoride compound:

Remineralization is a natural process to restore hydroxyapatite below the surface of the lesion that has not been freed from calcium and phosphate ions present in saliva [37]. Fluoride ions promote the formation of fluorapatite crystals, which are

more acid resistant and protect hydroxyapatite from degradation. Fluoride can be applied as prophylaxis mainly through toothpaste or varnish [38].

More recently, REFIX toothpaste has been developed with a biomimetic mechanism of PETA that combines fluoride, phosphate and silica to form a silicon-enriched layer of fluoridated apatite and hydroxyapatite, including dental tubules [39].

BIMIN is another technique that stimulates the orientation of enamel-like fluorapatite layers. This includes the diffusion of calcium ions from the phosphate solution and fluoride ions into the gel enriched with glycerine and forms a mineral layer that adheres to the surface of the teeth for eight hours [40].

4. The material filled with zinc oxide:

Zinc is commonly used in dental field and is incorporated to various dental products to reduce collagen degradation by MMPs (matrix metalloproteinases), and also to promote dentin remineralization [41]. Zinc is recognized as a bioactive component that enhances the self-healing ability of demineralized dentin. It promotes protein phosphorylation, increases calcium deposition, and stimulates the formation of crystal deposits that block the dental tubules. In addition, this crystal formation is resistant to degradation under acidic conditions leading to stable results [42].

5. DENTINE REMINERALIZATION

Demineralization is the removal of mineral ions from hydroxyapatite (HA) crystals in enamel, dentin, cementum, and bone. The restoration of lost mineral ions to demineralized crystals is called remineralization. Although significant mineral ions can be lost from HA without compromising its integrity, loss of sensitivity to heat, cold, pressure, and pain is expected, known as dentin hypersensitivity. If the integrity of the HA crystal lattice is lost, cavities appear. Demineralization is reversible, and demineralized HA crystals can return to their original size under favourable remineralization conditions [43,44].

a. Conventional approaches to crystallite's growth in remineralization:

Conventional remineralization procedures for affected dentin involve the use of formulations with varying concentrations of calcium and phosphate ions. In this scenario, remineralization occurs by epitaxial growth of residual apatite crystals in partially demineralized dentin rather than nucleation of new crystals [43,44]. If there are no or very few residual crystals, remineralization will not occur. The mineral composition of the superficial layer of the lesion affects the quality of the resulting remineralization, as well as the location and density of mineral deposits (Fig 1) [45].

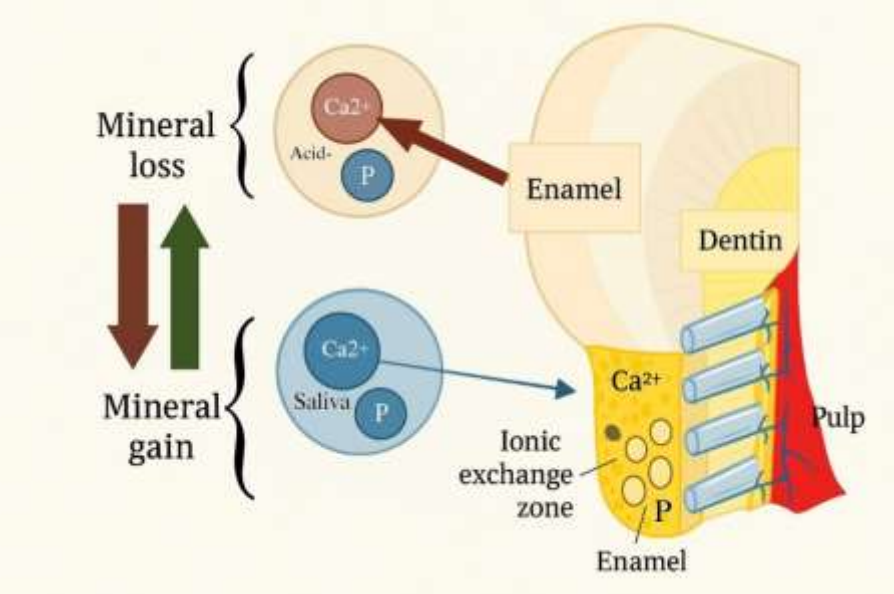

Fig 1: Demineralisation and remineralisation processes

b. Following a bottom-up biomimetic remineralization approach:

The biomimetic remineralization process involves the creation of insufficient nanocrystals to fill the gaps between collagen molecules in demineralized dentin. This top-down approach uses amorphous calcium phosphate (ACP) nano-precursor crystals stabilized with biomimetic analogs of non-collagen proteins (dentin matrix protein (DMP1) and dentin phosphoryl (DPP, DMP2)) that regulate the nucleation and growth of hydroxyapatite (HA) [46,47]. Various bioactive substances and analogs of non-collagen proteins (NCPs) have been used to promote remineralization (Fig 2) [48].

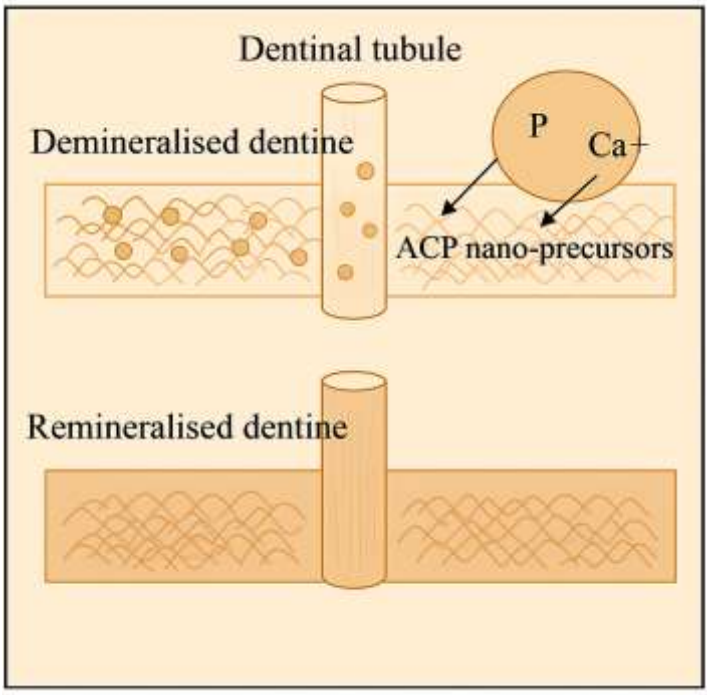

Fig 2: Bottom up biomimetic approach

6. NON-COLLAGEN PROTEIN (NCP) ANALOGUE-

The biomimetic remineralisation process involves the use of non-collagenous protein (NCP) analogues, including polydopamine (PDA) and polyelectrolytes.

a. Polydopamine:

PDA is a semiconducting polymer formed by the oxidation and polymerization of dopamine in aqueous solution [49] and can affect the remineralization of enamel and dentin. It acts as a nucleation site for biomimetic hydroxyapatite formation and can be used as a biomimetic coating for various restorative materials [50,51].

b. Polyamidoamine Dendrimer (PAMAM)

Dendrimers/Artificial proteins have biomimetic abilities and are widely used in medicine. They have a branched and spherical structure with numerous surface groups. PAMAM is a type of dendrimer that mimics non-collagenous proteins (NCPs) and is capable of promoting biomimetic intrafibrillar mineralization of dentin. It absorbs calcium and phosphate ions through its functional groups, thereby stimulating dentin and enamel remineralization [52]. PAMAM is considered a potent remineralizing material since it can sequester mineral ions and act as a template for nucleation [53,54].

c. Polyelectrolyte

Polyelectrolytes such as polyvinyl phosphonic acid (PVPA) and polyacrylic acid (PAA), are polymers with ionic groups that dissociate in aqueous solutions and become charged. PVPA stimulates intrafibrillar and interfibrillar remineralisation and acts as a protease inhibitor of MMPs in dentine, while PAA simulates the calcium phosphate binding sites of DMP1. These NCP analogues are crucial for biomimetic mineralization of dentine and preventing hybrid layer degradation during dentin bonding.

Moreover, PAA can stabilize metastable ACP nano-precursors that are small enough to infiltrate the demineralised collagen matrix [55,56].

d. Sodium trimetaphosphate (STMP)

STMP ($Na_3P_3O_9$) is an analogue of phosphophoryn that has the potential to phosphorylate collagen type I and create negatively charged sites that attract nano precursors. STMP is a biomimetic strategy for stabilizing and strengthening dentin through interaction with non-collagenolytic proteins, mineral nucleation and remineralization, and reducing collagen biodegradation.

7. BIOMIMETIC REGENERATION OF DENTIN-PULP COMPLEX

Untreated carious lesions can lead to inflammation and infection of the pulp, which may extend to the periapical tissues (57). Treatment strategies for this situation include vital and non-vital pulp therapies. Vital pulp therapy aims to stimulate dentin bridge formation to protect and isolate the pulp tissue. Non-vital pulp therapy involves root canal treatment, which includes debridement and cleaning of the tooth canals to remove diseased pulp tissue, followed by sealing the canals with an inert material to prevent microleakage [57].

The conventional method of treating necrotic pulp is problematic due to the increased risk of root fracture, pain, and secondary infections [58]. However, a modern approach to regenerate the dentin-pulp complex is by using biomimetic materials such as biomimetic cement, growth factors, stem cells, or scaffolds after disinfecting the root canal system. These materials and techniques have the potential to control signalling and differentiation of pulp cells, limiting inflammatory responses, and promoting tissue repair and regeneration, resulting in the deposition of new dentin-like hard tissue. Nevertheless, further research is needed to fully understand how the newly deposited dentin-like hard tissue can strengthen the pre-existing weak root [59,60].

8. BIOACTIVE INGREDIENTS

The dental ingredients that exhibit bioactivity stimulate local physiological responses through chemical or physical interactions, leading to chemical bond formation or tissue formation. Remineralizing bioactive materials, for instance, can promote the deposition of mineral-like substances on their surface when exposed to physiological fluids, induce remineralization, and facilitate normal tissue repair [61].

1. Calcium hydroxide ($Ca(OH)_2$)

It is a white, odourless, strongly alkaline powder (pH ≥ 12) that dissolves slowly in water. It was first mentioned in dentistry in the 1920s as a direct pulp capping material. In the aqueous medium, $Ca(OH)_2$ releases Ca^{2+} and OH^-, which is responsible for the antimicrobial and regenerative effects of hard tissues. The OH^- ions released by $Ca(OH)_2$ damage bacterial DNA and cytoplasmic membrane, increases pH, and activate the enzyme alkaline phosphatase to deposit calcium phosphate into the organic matrix of dentin, promoting dentin repair and calcification. The alkalinity of calcium hydroxide neutralizes the acidic nature of lactic acid which is secreted from osteoclasts, stopping the dentinal demineralization. A necrotic zone rich in calcium salts and calcium-protein complexes is formed due to direct contact of calcium hydroxide with pulp connective tissue, which stimulate the formation of compensative dentinal bridges.

$Ca(OH)_2$ is used in a variety of treatments including pulp capping, pulpotomy, apexification, canal disinfection of roots, tooth resorption therapy, furcation or root perforation, and horizontal fracture treatment.

Despite its limitations, such as poor sealing ability and rapid degradation, it is still preferred for many endodontic therapies due to its ease of handling and cost-effectiveness compared to other materials like mineral trioxide aggregate (MTA).

2. MTA – Mineral Trioxide Acetate

MTA is a calcium silicate-based hydrophilic cement that was developed by Torabinejad in 1993 as a modification of Portland cement. MTA is mainly composed of dicalcium silicate, tricalcium silicate, and tricalcium aluminate, along with radio-opacifiers to make it suitable for clinical use. Like other calcium silicate-based cements, MTA is biocompatible, bioactive, and exhibits a positive odontogenic effect on dental pulp cells and peripheral root tissues.

The bioactivity of MTA is attributed to the ability of calcium ions to react with phosphate in the presence of phosphate-buffered saline, forming a hydroxyapatite layer at the MTA-dentin interface. MTA is recommended for several dental applications, such as pulp capping, retrograde filling, apexification, and management of furcation and root perforations.

Compared to calcium hydroxide, MTA is more stable, has greater sealing ability, no moisture sensitivity, better handling, and more favourable outcomes in maintaining long-term pulp vitality. MTA Repair HP is a recently launched material that represents a calcium silicate-based cement with enhanced physical and mechanical properties and high biocompatibility with human pulp stem cells. It has proven bio-mineralization and antimicrobial activity.

3. Enamel Matrix Derivative (EMD)

It is a purified protein derived from the enamel layer of a developing porcine tooth germ cell. EMD contains mainly amelogenins (90%) and smaller amounts of enamelin, ameloblastin, amelotin, and other proteins. EMD plays a major role in the regeneration of the periodontal ligament, although its mechanism of action is not fully understood. Applying amelogenins onto a conditioned root surface forms an extracellular matrix with high affinity for hydroxyapatite and collagen, which interacts with surrounding cells and initiates regeneration. EMD can also induce reparative dentin in direct pulp capping and stimulate odontogenesis. Other uses include preventing implantitis, replantation cases, sealing root perforations, pulpotomy, and intracanal medication.

4. Biodentine

In 2009, the first biodentine product was introduced as a substitute for dentine. This bioactive material contains calcium silicate, which penetrates and interlocks with dentin to enhance mechanical properties. Biodentine powder includes tricalcium and dicalcium silicate, as well as minor constituents like calcium carbonate, iron oxide, and zirconium oxide. The liquid component consists of calcium chloride and a hydrosoluble polymer. Biodentine is commonly used for pulp capping, root perforation, apexification stimulation, and retrograde filling. It also induces odontoblast differentiation of human dental pulp stem cells and releases transforming growth factor (TGF-Beta 1), which leads to faster mineralization of pulp tissue. Biodentine has advantages over MTA, such as ease of handling, short setting time, high viscosity, and strength. It has a similar compressive strength to natural dentine and can establish high bond strength to different adhesive systems, making it useful as a dentine substitute material under adhesive bonded restorations.

5. Triple Antibiotic Paste

Triple Antibiotic Paste (TAP) is an ICM consisting of three antimicrobial agents that target the complete eradication of microorganisms from root canals and promote endodontic revascularization. Ciprofloxacin, which is highly effective against anaerobes, is combined with metronidazole to combat mixed infections. Metronidazole has demonstrated efficacy against the obligate anaerobes present in the necrotic pulp, while minocycline interferes with bacterial protein synthesis. The recommended clinical concentration of TAP is 1mg/mL (1:1:1), which has shown promising outcomes in the elimination of root canal microorganisms up to 99.99% and promotion of revascularization in immature permanent teeth. TAP's acidic pH demineralizes the dentin surface, enhancing the discharge of entrapped cytoskeletons of growth factors, dental pulp stem cell differentiation and proliferation, and surface roughness, which further facilitates stem cell differentiation and attachment. TAP concentrations higher than 1mg/mL have detrimental effects on dental stem cells. However, concentrations lower than 1mg/mL have no unfavourable effects on stem cell viability. Tooth staining due to minocycline can be prevented by using low concentrations of TAP and limiting it below the cementoenamel junction.

6. Bioceramics

Dentistry employs various types of bioceramics, including bioinert bioceramics like zirconia and bioactive bioceramics such as hydroxyapatite (HA) and calcium phosphate (CaP). Bioinert bioceramics are used for restorative applications, while bioactive bioceramics are used in endodontics and can be bioresorbable (e.g., CaP bone substitutes) or non-bioresorbable (e.g., calcium silicate or hydraulic cements). Bioactive materials trigger a positive reaction from host tissues by depositing a HA layer when exposed to calcium and phosphate-enriched tissue fluid. They possess excellent biocompatibility, osteoconductivity, osteoinductivity, and sealing ability. Gray mineral trioxide aggregate (GMTA), a commonly used endodontic material, contains bismuth oxide, tricalcium and dicalcium silicates, and is used for various applications such as vital pulp therapies, sub-osseous perforation repair, and root-end filling.

However, discoloration of teeth is a common side effect of using ProRoot mineral trioxide aggregate (MTA). A white MTA ProRoot, also known as white mineral trioxide aggregate (WMTA), was introduced to address this concern. Although MTA is the gold standard for root-end restorations, it has several drawbacks, including high cost, washout during irrigation, delayed setting, and difficult manipulation.

Biodentine, a relatively new material that contains zirconia, tricalcium silicate, and a radiopaque agent, has been developed as an alternative to MTA. It has similar indications to MTA but offers improved properties, and has shown good biocompatibility in various in vitro, ex vivo, animal, and clinical studies. The American Association of Endodontists recommends flooding root canals with blood via over-instrumentation with endo files or endo explorers to create a blood clot that can be replaced with platelet-rich plasma or platelet-rich fibrin in regenerative endodontic protocols. Biodentine has the potential to overcome the major concerns associated with MTA, such as discoloration, and may be preferred for anterior teeth where aesthetics is a primary concern.

9. CELL HOMING STRATEGIES

In 2010, cell homing strategies were introduced as a viable approach for dental tissue regeneration. These strategies involve recruiting stem or progenitor cells through chemotaxis via biological signaling molecules to achieve tissue regeneration and revascularization.

i. Platelet concentrates

Platelet concentrates occur innately in the body and plays an important role in tissue regeneration and healing of wounds. It is a group of peripheral blood-derived autologous biomaterials that offer several benefits, including ease of access, biocompatibility, less expensive, and revitalizing potential. This concentrate mainly contains platelets and fibrin, which are made up of biologically regenerative materials.

Platelet-rich plasma (PRP) was described in the 70s and is often used in several surgical procedures because of its ability to accelerate soft tissue healing. An ideal scaffold for regenerative endodontic treatment regimens is PRP because it can promote

cell growth and the release of growth mediators in a sterile environment.

Platelet-rich fibrin (PRF) is a 2nd generation platelet concentrate that has several pros than cons, over PRP, a simple and inexpensive preparation method and no need of adding exogenous anticoagulant compounds. They contain biological active proteins such as glucagon chains, cytokines and structural glycoproteins that are incorporated into the fibrin network and promote rapid wound healing and periodontal regeneration.

ii. Bone morphogenetic proteins

Bone morphogenetic proteins (BMPs) are dimeric molecules that belong to the transforming growth factor (TGF-ß) superfamily and consist of two polypeptide chains connected by a single disulfide bond. BMPs are present in bone matrix and demineralized dentin and play a key role in embryonic tooth development and cytodifferentiation. BMP2, BMP4, BMP5, BMP6 and BMP7 are involved in odontoblast and ameloblast differentiation. The scientists were able to use recombinant human BMP2 to stimulate the differentiation of pulp cells into odontoblasts and the formation of compensatory dentin. BMP-derived dentin regeneration can be stimulated by direct application of BMP to the pulp tissue to support natural healing. Another approach is to exogenously differentiate isolated progenitor stem cells and then transplant the differentiated odontoblasts into the tooth. Carriers, or operators, play an important role in facilitating the clinical use of BMPs and in ensuring the gradual distribution of BMPs to host tissues. They must be biodegradable and biocompatible.

iii. Hyaluronic acid (HA) and its derivatives

Dental pulp extracellular matrix (ECM) contains a major basic glycosaminoglycan component called HA. It induces regeneration due to its interaction with stem cell receptors and also plays a role in pulp tissue and dentin matrix development. In addition, hyaluronic acid byproducts promote odontogenic differentiation and mineralization of dental tissues. Although HA has properties such as biocompatibility, biodegradability, and bioactivity, its ability to regenerate is limited due to its low mechanical properties. To enhance its effectiveness, growth factors need to be added.

iv. Collagen

Collagen is a natural material that is both biocompatible and bioactive, and it closely resembles the extra cellular matrix. It promotes bioactive properties by enabling stem cells to adhere and attach, and by triggering signalling pathways that encourage differentiation.

Biomimicry Endodontics and Regenerative Approaches

Endodontics can benefit from biomimetic approaches, which include the use of biomaterials such as intra-canal medicaments, cements, and irrigation agents, as well as tissue regeneration strategies for dentin and pulp regeneration, and revascularization.

Endodontic Irrigation

Persistent microbial infections are the primary reason for conventional and regenerative endodontic procedure failures. Copious irrigation with disinfectants is required to eliminate microbial infections in root canals without damaging dental tissues. The ideal endodontic irrigants should have antimicrobial properties without harming the stem cells and normal tissues. Additionally, pulp remnants and necrotic tissues should be dissolved by irrigants for easy debris removal. Pulp necrosis can occur when the pulp becomes necrotic and microorganisms multiply, leading to the spread of infection and bone resorption. It is important that disinfection protocols do not harm the viabile stem cells, which are essential for endodontic regeneration. Sodium hypochlorite (NaOCl), chlorhexidine (CHX), ethylene diamine tetraacetic acid (EDTA), hydrogen peroxide (H2O2), and saline are commonly used as root canal irrigants. These chemical irrigants and intra-canal medicaments work together for the disinfection of root canals, reduce inflammation, and also promoting endodontic regenerative procedures.

Studies conducted in vitro have demonstrated that while EDTA and NaOCl do not harm stem cells, 2% CHX does. Concentrations of NaOCl greater than 1.5% have a negative impact on stem cell survival and differentiation, whereas a concentration of 1.5% has minimal effect on survival. On the other hand, 17% EDTA has a positive effect on stem cell survival. It has been demonstrated that CHX irrigation can have a negative impact on stem cell survival rates. However, this effect can be mitigated by reducing the duration of irrigation and neutralizing with L-a-lecithin.

Root Canal Medications

Root-canal medications (RCM) are used during endodontic treatment to eliminate any remaining microbes after cleaning and irrigation. Various ICM have been researched to ensure the elimination of microbes and prevent their regrowth in the empty pulp space. However, using high concentrations of ICM can harm dental pulp stem cells (DPSC) and stem cells from the apical papilla (SCAPs), which can negatively impact the success of regeneration in endodontics.

A study by Ruparel et al. examined the impact of triple antibiotic paste (TAP), double antibiotic paste (DAP), and calcium hydroxide (Ca(OH)2) on the survival of SCAPs in vitro. They discovered that all antibiotics, at different concentrations,

significantly decreased SCAP, while $Ca(OH)_2$ had a positive effect on SCAP in any concentration. Althumairy et al. found similar results, showing that exposure of dentin to TAP or DAP reduced SCAP viability. They also observed that treatment with $Ca(OH)_2$ led to a significant increase in both the proliferation and survival of SCAPs.

It is crucial to use an ICM with antibacterial properties that won't harm stem cells in terms of type and concentration. A combination of antibiotics is recommended because of the diverse nature of root canal bacteria.

- **Biomimicry Tissue - Engineering Aspects**

Biomimetic tissue engineering(BTE) is a concept proposed by Langer and Vacanti in 1993 to address issues related to organ transplantation such as donor scarcity, immunosuppression, and associated complications. It has become a hopeful method for regenerating nearly all organs and tissues. Its objective is to replicate the natural biological environment to restore or enhance unhealthy or injured tissues by reconstructing them or creating inherent biological systems.

B.T. Engineering is an interdisciplinary field that draws on expertise from areas like biology, chemistry, engineering, genetics, and physics. It applies three basic principles: implanting biomimetic scaffolds to aid cell differentiation, proliferation, and biosynthesis; promoting cellular adhesion with nearby tissues to produce new matrix; and delivering growth factors to support and enhance cell functions.

1. Ideal Characteristics of Scaffolds for Biomimetic Tissue Engineering

Biomimetic scaffolds are used to create a 3D microenvironment that offers structural support for cell adhesion, organization and vascularization. This leads to the growth, differentiation, and healing of cells, resulting in the formation of the desired or damaged tissue. The design of these scaffolds involves using various techniques, such as scaffold design, gene-based methods, and cell-based therapy, thereby replicate the structure and composition of the extracellular matrix.

Scientists worldwide have extensively investigated biomimetic, biodegradable, and bio-resorbable materials both experimentally and clinically to develop scaffolds with specific desired traits. However, designing the perfect biomimetic scaffold for tissue regeneration is a difficult task that requires meeting a variety of biological, mechanical and physical properties.

The scaffold used in tissue engineering must meet specific requirements to ensure it is biocompatible and non-toxic to the specific tissues. The native extracellular matrix can serve as a reference for achieving the desired physical and mechanical properties. E.g. in bone renewal, scaffold should have similar physical and mechanical properties as the bone tissue.

The biomimetic scaffold should be constructed to control the immune system by using immune-inert biomaterials that reduce the activity of B and T lymphocytes and natural killer cells through the concept of immuno-modulation.

Another important aspect of the biomimetic scaffold is its bioactivity, which promotes tissue neoformation through cell integration, differentiation, and migration. Bioactive glass scaffolds are made using different methods and encourage the formation of new tissue in the host.

Biodegradability is also crucial for the scaffold. The scaffold material should have a biodegradation rate that can be adjusted and controlled to match the tissue regeneration rate. It is important that the degradation products are eliminated without affecting other organs or causing toxicity.

2. Techniques for creating 3D biomimetic scaffolds

Biomimetic materials are created using a variety of techniques to design and produce fresh functional materials by altering their biological products functions, structures, and processes. Traditional methods have involved replicating the structures and functions of the extracellular matrix. However, recent developments have made it possible to build porous 3D biomimetic scaffolds with nanoscale precision for tissue regeneration.

There are 3 types of manufacturing procedures for 3D scaffolds:

a) Bioprinting (3D plotting or direct-writing), 3D printing (3DP), fused deposition modeling (FDM), stereolithography (SL), and selective laser sintering (SLS) are some of the rapid prototyping techniques.

b) The uses of porogens in bioactive materials are, gas-foaming, particulate-leaching, phase separation, solvent-casting, and freeze-drying.

c) Use of non-woven or woven fiber scaffolds through microsphere sintering and electrospinning.

3. B.T. Regeneration by Dental Stem Cell Therapy:

Regenerative tissue-engineering approaches require dental stem cells (DSCs). These cells are not fully developed and can change into different cell types as well as renew themselves. They are found in certain areas of each tissue, known as the "stem cell niche". Mesenchymal stem cells, also called multipotent mesenchymal stromal cells (MSCs), are a type of adult stem cell found in various tissues.

These cells have the ability to change into different cell types such as fat cells(adipocytes), cartilage cells(chondrocytes), bone cells(osteocytes), and other tissues. This makes them useful for regenerating damaged tissues. Stem cell therapy is a treatment that involves giving cells with the ability to regenerate to repair damaged tissues. There are several types of dental stem cells that come from different sources after birth, such as dental pulp stem cells, stem cells from baby(deciduous) teeth, and stem cells from the root tip (apical papilla) of teeth.

New technologies like reprogramming stem cells and transferring the nucleus of a body(somatic) cell into an egg cell can turn mature cells back into an embryonic-like state, avoiding problems with the immune system rejecting embryonic cells.

Using stem cells to rebuild damaged structures in the mouth shows potential, but it's important to know how stem cells change and develop to use this treatment safely and effectively.

10. CONCLUSION AND FUTURE TRENDS

The development of biomimetic restorative biomaterials has been a subject of extensive research in recent years, with scientists modifying existing materials or developing new ones. Processing technologies such as nanotechnology, fabrication methods, and functionalization of biomaterials have been explored to produce biomimetic materials with properties that simulate those of natural tissues. While there have been significant advancements in biomimetic restorative materials in the past decade, the complex nature of dental tissues means that this field is still in its early stages. Similarly, while biomimetic tissue engineering has grown exponentially, more research is needed to translate these developments into practical and clinical applications.

Despite the challenges, new treatment modalities are likely to emerge in the near future, with regeneration of dentin, enamel, pulp, restorative procedures, and management of soft tissues of periodontium becoming possible. The development and translation of smart biomimetic dental restoratives from lab to clinical dentistry also holds great potential, although there are still challenges and limitations to overcome.

To further advance this field, there is a need for an expansion of knowledge related to biological and biochemical mechanisms of biomineralization. Novel biomaterials with innovative biomimetic cell-free templates, intrinsic disordered protein, and peptide-based remineralization strategies also hold promise. Additionally, the role of various biomimetic agents and molecules involved in tooth tissue regeneration require further investigation. Interdisciplinary research is underway to address these challenges, and it is hoped that completely regenerated dental tissues with biological, mechanical, and mineralized nano-structural properties that mimic natural tooth tissues will be available in the future.

Abbreviations:

1. **3Y-TZP** - 3-Mol % yttria partially-stabilized tetragonal zirconia polycrystal
2. **ACP** - Amorphous calcium phosphate
3. **BAG** - Bioactive glass
4. **$Ca(OH)_2$** - Calcium hydroxide
5. **CAD/CAM** - Computer-aided design/computer-assisted manufacturing
6. **CPP-ACP** - Casein phosphopeptide amorphous calcium phosphate
7. **DCR** - Dental composite resin
8. **DMP** - Dentin matrix protein
9. **GIC** - Glass-ionomer cement
10. **HA** - Hydroxyapatite
11. **MMPs** - Matrix metalloproteinases
12. **MTA** - Mineral trioxide aggregate
13. **NCPs** - Non-collagenous proteins
14. **PAA** - Polyacrylic acid
15. **PAMAM** - Polyamidoamine dendrimer
16. **PAPE** - Phosphoric acid polyethylene
17. **PDA** - Polydopamine
18. **PICN** - Polymer-infiltrated ceramic network
19. **STMP** - Sodium trimetaphosphate

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