Biomimetic materials and its biomedical applications in dentistry: A literature review

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Abstract

Biomimetics has transpired into a multidisciplinary approach in the dental medicine. Nowadays, these matter have acquired lot of popularity and exhibited excellent results with treatment outcome. The biomimetic accession has been activated for variety of applications in restorative dentistry. They have been utilized for building up of tooth-tissue defects with the help of bioregenerative materials for tissue engineering, bioactive biomaterials and bioinspired peptide compounds for re-mineralization. The various Biomimetic materials used in dentistry are categorized into metals, ceramics, polymers and composites. This article highlights the

implementation of the biomimetic approaches of various materials and its implications in dentistry in various aspects.

Keywords: Biomaterials; restorative dentistry; polymers; ceramics

Introduction

Biomimetic is a branch which deals with multidisciplinary mechanisms and biomaterials to fabricate products which are caricature in nature. The term biomimetics a coined by a biophysicist Otto Schmitt in the 1950's. [1] Biomimteic materials has progressed as a new entity which has transfigured the shape of dentistry [2]. These biomimetics are available as natural or synthetic which promote the repair process [2,3]. The contemporary biomimetics have certain characteristics like biocompatibility, bioesthetics, bioregenration etc which mimics the natural teeth resulting better treatment success. These biomimetic materials are incorporated in restorative materials, implants and prosthesis, direct and indirect restorations, and regenerative approaches [3]. Functions of biometically repaired teeth are comparable to those of native dentin. [4]. These restorations are inexpensive, have increased longevity, highly esthetic and reduced post-operative sensitivity as compared to earlier restorations [4]. Biomimesis is a concept which facsimiles the philosophy of fabricating materials in a favorable environment which replicates nature [3,4].

Types of Biomimetic materials

1. Glass ionomer cement (GIC):

   Developed in 1969, glass ionomer cements are comprised of fluoroaminosilicate powdered glass and water-soluble acids. Once the powder is blended with liquid, hardening reaction occurs involving neutralization of acidic groups releasing fluorides. [5] Bioactive glass and hydroxyapatite are the main components of bioequivalent combinations like 45S5 and S53P4. The inclusion of particular alloys, such SS, and ceramics, like zirconia, has improved the strength and mechanical qualities of GIC. [6] GIC sealers like KT-308 (GC Corporation Company, Tokyo, Japan) prevents the coronal penetration of bacteria much better than zinc oxide eugenol sealers.[7] GIC sealer has been found to be effective in treating chronic apical periodontitis when paired with antibacterial silver-containing zeolite (ZUT, University of Toronto, Ontario, Canada). [8] Glass ionomer impregnated Gutta Percha cones termed as Active GP (Brasseler USA, Savannah, GA, USA) are able to bond well to GIC sealers and provides better adhesiveness of active GP with intraradicular dentin. [9,10]

2. Resin Based Composites

   R. L Bowen, in 1962 introduced composites proffered with good resistance to wear, better esthetics, good radiopacity and improved physical properties. But however, with the advancing technology, variety of nanocomposites were developed which had better mechanical and physical properties than the traditional composites. Hence, different nanocomposites are enlisted in Table 1.

MODIFIED NANOCOMPOSITES	MATERIALS USED
1. Reinforced Fillers	• Nano fibers with electro spun nylon consisting of silicate single crystals which are highly aligned • E-glass fibers and nano fibers containing baal silica in semi-interpenetrating polymer network (IPN) matrix. • Titanium dioxide embedded nano composites crosslinked with Allytriethoxysilane (ATES)
2. Fillers for Caries prevention	• Nano-dicalcium phosphate anhydrous whiskers composites • Tetracalcium phosphate (TTCP) having calcium phosphate whisker • Calcium fluoride nanoparticles with reinforcing whisker fillers • Polymer-kaolinite Nano composite
3. Modified Resins	• Epoxy resin ERL-4221 (3,4-Epoxycyclohexylmethyl-(3,4-epoxy) cyclohexane carboxylate) • Epoxy functionalized cyclic siloxane • Silsesquioxane (SSQ) • Epoxy-polyol matrix • Bioactive poly i.e. methyl methacrylate/SiO2-CaO Nano composite
4. Nanoparticles surface modified with silanes	• Allytriethoxysilane (ATES) • Equal masses of MPTS and MPTS • Dual salinization with MPTS and OTMS • n-octyltrimethoxysilane (OTMS) • 3-methacryloxypropyltrimethoxysilane (MPTS) • γ glycidoxypropyl trimethoxysilane (GPS)

Table 1: Evolution of Nanocomposites

Smart Dentine Replacement (SDR) is considered as a dentin substitute. SDR is a flowable composite which is readily used owing to its high penetration depth while curing, less polymerization shrinkage, and can be used for bulk-fill in Class I and II cavities upto a depth of 4mm. [11-13].

3. Ceramics

Ceramics are considered as amalgamation of non- metallic and metallic salts like oxides, silicates, and nitrides. They are available in two forms- amorphous (glass) and crystalline [14,15].

The compilation of covalent and ionic and bonds in ceramics turn them into stiff and brittle materials [16]. They are defiant to compressive stresses but, cannot withstand tensile and shear stresses [17]. Ceramics are translucent and opaque depending on their crystalline architecture. More the amorphous phase, ceramics turn translucent and ceramics appear opaque when the crystalline phase is more [18]. These materials are tough and biocompatible [19].

Hydroxyapatite (HA) is calcium – phosphate ceramic, which are highly recommended to be used in medical and dental fields. It is used as a bone replacement material because of the chemical bond formed once it is implanted [20,21]. Properties like bioactive, biocompatibility, osteoconductivity, and high compressive strength makes it a favorable choice in these fields [22].

Ceraball, a ceramic bone substitute material has shown to have profound results in the field of tissue engineering helping in osteogenesis on the scaffold surface. Multipotent mesenchymal stem cells, stromal cells, and bone marrow are also transported by it. [23] Fig 1 depicts the applications of ceramics in the field of dentistry.

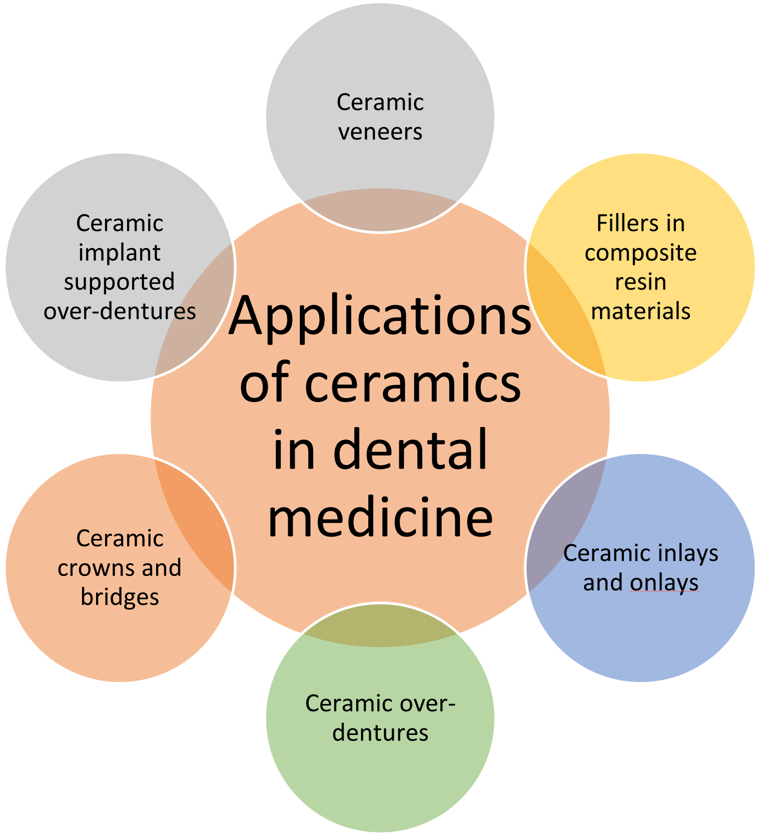

Figure 1: Applications of ceramics in dental medicine

4. Calcium Hydroxide:

Herman introduced calcium hydroxide to dentistry in 1928. It was considered as the benchmark material for pulp capping procedures. It is commonly utilized as a mineralizing and antibacterial agent because of its alkaline nature and reparative dentin development. There are two different types of dentinogenesis depending on whether the odontoblasts retain the insults or become deformed by them. Reactionary dentinogenesis takes place when the tertiary dentin is formed by the focally stimulated antecedent odontoblasts, and reparative dentinogenesis occurs when the tertiary dentin is laid down by new entity of secretory cells after the demise of primary odontoblast. [24] $Ca(OH)_2$ is also widely used in endodontics as intracanal medicament, closure of open apex or apexfication procedures [26, 27]. This material can neutralize lactic acid produced by osteoclasts preventing tissue destruction and releases growth factors aiding in pulpal repair [28, 29].

Calcium Sulfate is one of the prototype of calcium hydroxide has proven to be osteoconductive, bio-absorbable, permits fibroblast migration, biocompatible, and does not increase the blood calcium levels. Recently, granular version of calcium sulfate with poly-l-lactic acid is invented to reduce the rate of degradation. [30]

Calcium Phosphates play a pivotal role in physiologic and pathologic mineralization. They are commonly used in the form of cements, pastes, scaffolds and ceramics. Variable categories of calcium phosphate materials are listed in Table 2. [31]

CALICUM PHOSPAHTE MATERIALS	VARIOUS FORMS
1. Calcium phosphate combined with ceramics	• Beta-tricalcium phosphate [synthograf, augment (miter, Inc.] • Biphasic calcium phosphates [triosit (Zimmer)] • Calcium hydroxyapatite [calcitite (calcitek, Inc.)]
2. Calcium phosphate materials extracted from natural products	• Bio-oss (extracted from sintered bovine bone) • Coralline ha [interpore 200 (interpore)]
3. Calcium phosphate glass ceramics	• Bio glass (American biomaterials corporation)

Table 2: Various forms of calcium phosphate materials

Calcium Enriched mixture (CEM), another calcium formulation consisting of sulfur trioxide, calcium oxide, silicon dioxide, and phosphorous pentoxide. It has been thought to promote cementum formation and multiplication of stem cells. [32]

Calcium silicate based materials/ Bioceramic based material/tricalcium silicate, is another type of calcium product. The various calcium silicate materials are classified as:

a. Mineral Trioxide Aggregate (MTA): MTA as introduced by Mahmoud Torabinejad. It was originally formulated as Portland cement as root repair material. It was later modified to MTA, composed of bismuth oxide for radio-opacity, calcium sulphate, calcium aluminoferrite, calcium aluminate, and silicate of calcium. Clinical applications include apexification, apicectomy, deep caries management, retrograde root end filling, and repair of perforation sites [30,31]. Various studies have shown that the necrotic zone formed with MTA was less caustic than calcium hydroxide [32, 33].

There are four types of MTA formulations which are enlisted in Table 3.

MTA Formulation	Description
MTA fillapex (angelus solutions odonatological, Londrina, PR, Brazil)	A calcium silicate bioceramic root canal sealer which was developed to improve the strength of the sealer and biocompatibity of MTA. [33,34]
2. MTA angelus (Aangelus, Londrina, PR, Brazil)	Consists of 20% bismuth oxide and 80% Portland cement which has a setting time of 14mins. [35,36]
3. Pozzolan cement (Endocem) (Maruchi, Wonju, Korea)	Rapid set material obtained from MTA and does not comprise any chemical accelerator. [37]
4. MTA plus (Avalon biomed Inc., Bradenton, FL, USA)	Diaphanous powdered RC sealer with the ingredients indistinguishable to Proroot MTA. [38]

Table 3: Types of MTA formulations

b. Calcium Aluminate Cement (Binderware, São Carlos, SP, Brazil): This cement was produced by Federal University of São Carlos. It consists of iron oxide, silica, calcium oxide, magnesium oxide and alumina.[39,40] These cements manages the action of certain impurities like iron oxide which results in tooth discoloration and since they are free of MgO and CaO preventing material expansion when in contact with saliva or moisture. [41,42]

c. Biodentine ™ (Septodont, Saint-Maur-des-Fossés, France): This material is comparable to MTA which liberates calcium ions, activates formation of reparative dentin, antimicrobial and biocompatible material [43]. Biodentine is commercially available as powder and liquid. Calcium carbonate, Di and tri calcium silicate, iron oxide and zirconium oxide, constitutes the powder compartment. $CaCl_2$ (accelerator) and a hydrosoluble polymer (water reducing agent) form the liquid part. Since the mechanism of action closely resembles to calcium hydroxide, biodentine can be employed for deep caries management, apicoectomy, and apexification procedures. It has been demonstrated that biodentine, when combined with dentine, produces "Mineral Infiltration Zone," or tag-like structures next to the interfacial layer, which enhances the adhesive qualities. [44]. It has enhanced physical characteristics, a shorter setting time (12 minutes), and it encourages the proliferation of cells similar to odontoblasts and mineralization. [45].

d. Bioaggregate (BA) (Innovative Bioceramix Inc., Vancouver, BC, Canada): Dicalcium silicate, tricalcium silicate, monobasic Ca3(PO4)2, amorphous SiO_2, and tantalum PO_4 (radiopacifier) are used to make nanoparticle powder, while deionized water is used to make the liquid component. This formulation is aluminum free, stimulating the multiplication of human PDL fibroblasts and assists regeneration of periodontal tissues.[46-49]

5. Endosequence Root Repair Material (ERRM) putty, ERRM paste RRM putty fast set (FS) and iroot FS: This substance is offered as an intranasal medication in the forms of preloaded syringe paste and moldable premixed putty (iRoot BP Plus). It consists of monobasic calcium phosphate, zirconium oxide, calcium silicates, and tantalum oxide.[32, 50,51] It forms tag like structures inside the dentinal tubules. [45] RRM's helps in the growth of the gingival fibroblasts on the surface. [46,47] RRMs, which can be distinguished from MTA, bioaggregate, and Biodentin, are single component, premixed materials that can be utilized straight from the syringe or a small screw-cap box without the need for mixing. The first setting time for RRM putty Fast Set (FS) is 20 minutes. [46,52] A line of materials called iRoot FS (Brasseler USA, Savannah, GA) has better handling qualities and a quicker setting time.[32,53]

6. Bioceramic sealers

a. Bioceramic Gutta-Percha: These gutta percha cones have bioceramic nanoparticles incorporated within and on the surface that have been laser-verified for tip and accuracy. This "threedimensional" bonded healing is made possible by these cones with ingested bioceramic sealers. [32]

b. Endosequence BC sealer ((Brasseler USA, Savannah, GA) or iRoot SP root canal sealer (Innovative Bioceramix Inc., Vancouver, BC, Canada): This root canal sealant is already mixed and contains the following bioceramic ingredients: ZrO_2, di- and tri- calcium silicate, monobasic Ca3(PO4)2, colloidal silica, calcium silicates, and $Ca(OH)_2$ [54]. A few properties of the iRoot SP include alkaline pH, water loving, and enhanced calcium hydroxide release. [55]

7. Bioactive Glass (BAG): In restorations, mouth prophylaxis, polishing processes, desensitising toothpastes, bonding, and bone regeneration, calcium sodium phosphosilicate is used [56–58]. BAG fragments were combined with 50% bismuth oxide and utilised for root canal obutration in a study by Mohn et al. BAG has demonstrated antibacterial activity that is pH dependent. [59]
8. Re-mineralizing substances:

a. Casein phosphopeptide amorphous calcium phosphate (CPP-ACP): It is possible to try to remineralize subsurface carious surfaces by diffusing Ca and PO_4 ions into the tooth substrate. The primary phosphoprotein in cow's milk, caesin has sensory qualities. Calcium and phosphate are balanced in soluble form by CPP, which also serves as a source of both nutrients.[56] The improved mechanical, compressive and microtensile bond strengths, Ca, PO_4, and F ions are released when CPP nanoparticles are crosslinked to GIC. [60] 10% of the weight of either MI PasteTM (USA and Japan) or Tooth Mousse TM (Europe and Australasia) is made up of CPP-ACP nanocomplexes. [56]
b. Demineralized dentin (dDM) is a dentinal matrix that is used as an implant biomaterial and has the capacity to promote osteogenesis and chemotaxis. Chromogenesis and osteogenesis are triggered when dDM comes into touch with mesenchymal cells. [61] Enhancing biochemical and biomechanical characteristics is achieved by incorporating Galla chinensis extract into the dentinal matrix. [62]
c. Enamel matrix derivative (EMD): This is constructed from porcine enamel matrix (Emdogain; Straumann AG, Basel, Switzerland), and it has been used to gradually restore the functionality of PDL, cementum, and alveolar bone in cases of grade III attachment loss by engaging cementoblasts on the root surface. [63]
d. Growth Factors: These chemicals are essential for the healing of wounds. Neutrophil chemotaxis, which is aided by platelet-derived growth factor (PDGF), results in the production of collagen when it interacts with other GFs. The KGF, in conjunction with keratinocyte differentiation, is crucial for the re-epithelialization of wounds. Collagen synthesis and extracellular matrix deposition are induced by transforming growth factor (TGF). The FGF promotes matrix synthesis, ontogenesis, and fibroblast differentiation. At the capillary level, VEGF enhances vascular leakage. The behavior of EGF is autocrine. [64] The KGF-2 agonist ketivance aids in the prevention of oral mucositis. For all surgical wounds, Juvista, a recombinant TGF-b3, is administered as a growth factor reinforcer. [64]

e. Bone Morphgenic Proteins (BMPs): BMPs are recognized to be essential in osseous grafting for implant insertion, fracture remodelling, and spine fusion. It promotes brain cell development, alkaline phosphatase activity, proteoglycan biosynthesis in chondroblasts, collagen anabolism in osteoblasts, and monocyte chemotaxis. In high risk individuals, BMP-2 and BMP-7 are better to autologous bone transplantation. [65]
f. Platelet Concentrates: The first description of platelet concentrates was by Whitman et al. [66] A great pedigree of several growth factors, including PDGF, TGF-B, and IGF-1, which modulates wound healing, is PRP, which is obtained using differential centrifugation. Unlike PRF, PRP requires biochemical blood management along with anticoagulants, whereas PRF does not. [67] Choukroun's second-generation platelet concentrate, leucocyte and platelet rich fibrin (L-PRF), is devoid of gel-forming agents and anticoagulants. [68,69]
g. Polyhedral Oligomeric Silsesquioxanes (POSS): By combining POSS molecules, bioactive substances including polyhedral oligomeric silsesquioxanes (POSS) and polyhedral oligomeric silicates (POS) are created, providing a nanoscopic topography that serves as a reservoir for cellular regulation, bioavailability, and differentiation. The creation of dentin adhesives and composites with superior physical and mechanical properties has been made possible thanks to POSS. [70]

9. Metallic Biomaterials: These biomaterials are used to create medical equipments for the substitution of hard tissues, such as dental implants, prosthetic hip joints, and bone plates. These applications frequently involve the use of stainless steel (SUS 316L SS, an austenitic stainless steel), cobalt alloys, pure titanium, and Ti-6al-4v. [71,72] Implant Biomaterials/Biomimetic Coatings on Implants: Implants are made using metals, metal alloys, ceramics, organic substances, and artificial polymers. Tantalum, Ti, and the alloys Ti-Al-Va, Co-Cr-Mb, and Fe-Cr-Ni are examples of metals and metal alloys. Hafnium, tungsten, and zirconium implants have recently been evaluated. [73] Robotic processes are used to create the coating on metal that is coated with hydroxyapatite. [73]. Some beneficial substances include the Arg-Gly-Asp tripeptide, protein kinase A, bone morphogenetic protein-2 (BMP2), and phospholipase A2 [73].

10. Polymers

    With the upcoming latest materials in dentistry, polymers are becoming demanding. One of the most widely used polymeric base material is exclusively employed in complete and partial denture fabrication. Various dental materials like pits and fissure sealants, resin cements and denture liners, consists of polymers [74]. However, PMMA is considered as the gold standard for denture bases. PMMA are easy to repair, less cost effective, easily available, less soluble, and easy to fabricate. Biggest disadvantage of PMMA is that it readily fractures due to high impact strength [75].

    Offlate polymers are being used in tissue engineering and regenerative approaches. Research has shown that the employment of poly lactic-co-glycolic acid (PLGA) in extraction socket before the placement of metallic implants helps in healing of the alveolar socket and ossification [76-78].

In tissue engineering, Polymers are employed as delivery vehicles for the embedding of growth factors. These growth factors are marked with polymers and carried to the desired spot for the prolonged release [79].

11. Smart Materials:

They are the materials that are naturally able to adapt to changes in the environment and are very perceptive. Active and passive smart materials are divided into two categories. Active smart materials use a feedback loop to assist them behave like a cognitive response using an actuator circuit, whereas passive materials react to external stimuli without any external force. [80] Table 4 depicts the various smart materials in dentistry

Smart materials	Description
a. Smart pressure bandages	As these bandages come into touch with blood, they shrink and provide pressure to the wound.
b. Smart suture:	This suture material forms a flawless knot on its own and has shape memory.
c. Hydrogel	Changes in temperature, pH, magnetic field, or electric field cause this intelligent material to contract plastically.
d. Amorphous calcium phosphate-containing smart composites (ACP)	ACP is incorporated into composite materials to aid in the long-term, sustained release of calcium and phosphorous, avoiding cavities.
e. Cercon	Smart ceramics: Metal free smart material, which is biocompatible and produces life like restoration resisting crack formation. The disadvantages of PFM, which are not an issue with Ceron, are dark margins and synthetically created grey silhouette from the concealed metal.
f. Smart fibers for laser dentistry	Using hollow-core photonic crystal fibres (PCFS), high-fluency laser radiation capable of ablating tooth structure is carried. These PCF fibres assist in transmitting plasma emission onto tooth surfaces for optical and investigative diagnosis. [80]

Table 4: Types of Smart materials in dentistry

12. Bioresorbable materials: These materials dissolve and get replaced with tissues like bone. These materials get hydrolyzed into smaller particles through enzymes or hydrolytic approaches. This

entity of bioactive materials is extensively used for regenerative medicine approaches. Polylactic acid, Cellulose, acetate, nitrocellulose, etc are included in this category of materials [3,4].

Conclusion

Biomimetic materials is recently included in dentistry which restores and repairs the tissues is the most natural aspect. The characteristics and properties of biomimetic materials similitudes the tooth structure helping to restore the tissues in a natural way. These biomimetic materials are well equipped with genetic engineering strategies like pulp regenerative techniques and approaches. This paper apotheosis the applications and implications of biomimetic materials in dentistry.

Abbreviations

- **GIC:** Glass ionomer cement
- **SDR:** Smart Dentine Replacement
- **HA:** Hydroxyapatite
- **Ca(OH)2:** Calcium Hydroxide
- **CEM :** Calcium Enriched mixture
- **MTA :** Mineral Trioxide Aggregate
- **MgO :** Magnesium oxide
- **CaO :** Calcium oxide
- **$CaCl_2$:** Calcium Chloride
- **BA** : Bioaggregate
- **Ca3(PO4)2 :** Calcium Phosphate
- **ERRM putty:** Endosequence Root Repair Material
- **CPP-ACP** : Casein phosphopeptide amorphous calcium phosphate
- **Ca, PO4, and F ions**: Calcium, Phosphate and Fluoride ions
- **dDM** : Demineralized dentin
- **EMD** : Enamel matrix derivative
- **PDGF**: Platelet-derived growth factor
- **GF**: Growth Factor
- **PDL** : Periodontal Ligament
- **KGF** : Keratinocyte Growth Factor
- **TGF** : Transforming growth factor
- **FGF** : Fibroblast Growth Factor
- **VEGF**: vascular Endothelial Growth Factor
- **BMPs** : Bone Morphgenic Proteins
- **PDGF** : Platelet Derived Growth Factor
- **TGF-B** : Transforming Growth Faactor -Beta
- **IGF-1**: Insulin-like growth factor- 1

- **PRP**: Platelet Rich Plasma
- **PRF**: Platelet Rich Fibrin
- **POSS**: Polyhedral Oligomeric Silsesquioxanes
- **POS** : Polyhedral oligomeric silicates
- **Ti** : Titanium
- **Ti-Al-Va :** Titanium- Aluminium - Vanadium
- **Co-Cr-Mb :** Cobalt – Chromium - Molybdenum
- **Fe-Cr-Ni :** Iron- Chromium – Nickel
- **PMMA:** Poly(methyl methacrylate)
- **PLGA :** Poly lactic-co-glycolic acid
- **ACP:** Amorphous calcium phosphate

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