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Review Article

Polymer-Ceramic Bionanocomposites for Dental Application

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Multiphasic bionanocomposites have been highlighted in the biotechnology field since they have offered mechanical flexibility during operation. This interest has been increased mainly through polymer/ceramic/metal manipulation techniques and modifications in formulation. Recently, a number of studies on bionanocomposites have been examined due to their favorable mechanical properties and cellular activities when compared to the neat polymers or polymer blends. This paper critically reviews recent applications of bionanocomposites for regeneration of pulp-dentin complex, periodontal ligament, and alveolar bone, and substitute of enamel in dentistry.

1. Introduction

With the development of nanotechnology, bionanocomposites have significantly contributed to the biotechnology over the past 20 years [1]. Multiphasic nanocomposite consists of solid inorganic materials on the organic matrix [2] and is classified into three categories: ceramic, metal, and polymer nanocomposites. When inorganic materials are incorporated into the organic matrix, called polymer-based nanocomposites or just nanocomposites, it represents a new class of biomaterials with much more powerful performance than their monophasic counterparts [3]. Interest in the use of bionanocomposites has been increased mainly through polymer/ceramic/metal manipulation techniques and modifications in formulation, and their use has been marked in particularly dentistry [4]. As a dental material, bionanocomposite mimicking native tissue structure and properties is able to endure high biting force and harsh environment in which there exists a sudden change of temperature or osmotic pressure by various types of food and invasion of various pathogens [5]. Similar structure or properties to bionanocomposites are often found, for example, in the alveolar bone, dentin, and enamel and therefore expected their promising use in dentistry.

Bionanocomposites are fabricated in the polymer matrix, which serves as a potential biological carrier to recruit resident cells [6]. As a matrix material, biopolymers include excellently biocompatible collagen, alginate, silk, polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), and polycaprolactone (PCL), but some of them are mechanically fragile, often provoke immune responses, and are still not satisfactory in terms of cellular activity [6–9]. To deal with this, inorganic materials have been employed when fabricating nanocomposites, which have significantly increased the mechanical or surface properties as well as favor cellular response [3]. These inorganic materials include bioactive glass nanoparticles, magnetic nanoparticle, carbon nanotubes (CNTs), hydroxyapatite, silver or gold nanoparticles, graphene oxide (GO), titanium oxide, and silica nanoparticles [10]. This paper critically reviews applications of bionanocomposites recently used in dentistry (Figure 1).

2. Characteristics of Bionanocomposites

2.1. Mechanical Properties. The main reason for incorporation of inorganic materials on the polymer matrix is to improve mechanical properties (including tensile strength, flexural strength, hardness, Young's modulus, or stiffness) [11, 12]. As a dominant mechanism, microcrack toughening is considered to increase mechanical properties of nanocomposites. This acts ahead of the crack tip to increase the material's toughness,

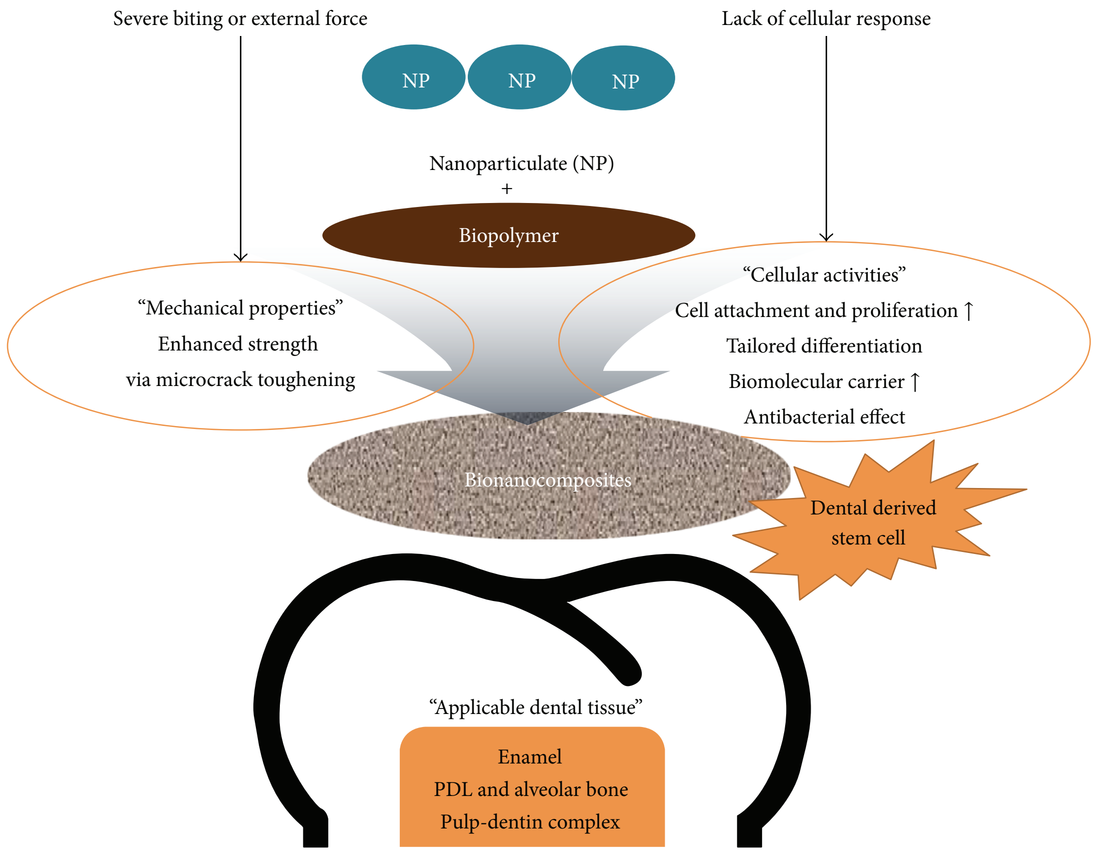

FIGURE 1: Application of bionanocomposites for dental tissue regeneration (periodontal ligament (PDL) or pulp-dentin complex) or substitute (enamel). Inorganic nanoparticle and organic biopolymer are combined toward bionanocomposite, expecting to enhance mechanical properties as well as cellular activities.

which is called intrinsic toughening mechanisms. The initiation and development of large number of microcracks around inorganic nanoparticles and consequently the increase in the fracture surface area are the major defense for further crack growth due to crack deflection [13]. Conversely, as an extrinsic toughening mechanism, it was reported that crack bridging impedes the crack growth behind crack tip, and crack-tip interaction changes direction of crack growth and increases fracture surface area, which is considered to act behind the crack tip to resist its further opening [14]. From the results of mechanical tests, the tensile strength, modulus, and yield strength of the bionanocomposites consisting of PCL and silica were enhanced up to 10% by the incorporation of silica nanoparticles [15]. Tensile test data showed that Young's modulus of PLA/organoclay nanocomposite was about 19% higher than that of neat PLA [11]. The incorporation of 5 wt% of GO rendered the nanocomposite mechanically ~2.5-fold and ~4.7-fold higher than the tensile strength and Young's modulus of PLGA, respectively [12]. Incorporation of ionically modified carbon nanotubes into PCL-HA composition significantly enhanced elastic modulus and the compressive strength of the robotic-dispensed scaffolds (~2.5-fold in elastic modulus and ~1.5-fold in strength) [16].

2.2. Biological Properties. While the bionanocomposites are able to provide proper mechanical properties of scaffolds for dental tissue regeneration, their biocompatibility can be maintained for the dental application. Only a concern about safety issue was able to be raised due to released nanoparticles into the human body or the environment when used in dental application. However, evidence for acute toxicity from nanomaterials at realistic doses is limited and there is no simple correlation between nanoparticle size and toxic responses [17]. At the moment, there is still no consensus on the toxicity of nanomaterials, and therefore nanosafety is always considered when bionanocomposites are used in dentistry.

Although many biopolymers have been confirmed as demonstrated by biocompatibility tests, they still lack the necessary cellular characteristics for regenerative medicine. To overcome their limitations, additional inorganic nanomaterials are integrated into the architecture to form a bionanocomposite [18]. As a result, bionanocomposites showed favorable interactions between the cell membrane and material surface. Additionally, they enabled spatially controlled protein binding for cellular adhesion, nucleation of mineralized matrix, or provided vital factors for the motivation of stem cells toward specific lineages. Incorporation of inorganic nanomaterials altered the differentiation status of stem cells and acted as nucleation sites for the deposition of mineralized matrix [19]. These modifications can employ bioinspiration via mimesis of naturally occurring molecular processes or microenvironment induction of cellular behavior. Also, degradation of networked polymer composites was retarded to the point of occurring sufficient cell migration and tissue formation in vivo.

In one biomaterial regime, bioactive glass nanoparticles have shown excellent biological activity in relation with bone-derived cells and tooth-derived cells, such as odontoblasts and dental pulp cells [20]. They had poor mechanical properties, such as high brittleness and low tensile strength, and were difficult to process, which primarily restricted their practical applications as scaffolds for dental tissue engineering. However, the class of bioactive glass nanoparticles have a lot of advantages such as osteoinductive properties, regulating genetic profiles of osteoprogenitor/stem cells down to the lineage of bone forming cells [11]. Therefore, the composite approach of using biopolymers in concert with bioactive glass nanoparticles is considered promising strategy to attain cell matrices with physic-chemical and biological properties appropriate for hard tissue engineering.

Among the nanoparticulate additives, magnetic nanoparticles (MNPs) have recently gained great interest [21], due to their superparamagnetism properties [22–24]. When MNPs were added to the biopolymer matrix, the bone cell attachment, growth, and differentiation were improved [23, 25]. Moreover, MNP-biopolymer matrices for dental pulp regeneration enhanced dental pulp stem cells (DPSCs) adhesion, growth, migration, and odontoblastic differentiation regarding pulp regeneration with local magnetism induced integrin signaling with FAK/MAPK and NF-κB activation [26].

Graphene (G) and its oxidized form GO materials are available as biomaterials with high stiffness and affinity to cell or biomolecules, which can potentially serve as a biocompatible, transferable, and implantable platform for dental or bone-derived stem cell culture [27, 28]. The healthy proliferation of stem cells on G and GO matrices was demonstrated a lot. It was also reported that the strong noncovalent binding abilities of G allowed it to act as a predisposition platform for osteogenic or odontogenic inducers, which accelerated stem cell growth and differentiation into the osteogenic or odontogenic lineage. Interestingly, differentiation into adipocytes was greatly suppressed on G because one of the key regulators for the synthesis of fatty acids was denatured upon π-π adsorption on G, but not in GO [29]. However, GO is relatively dispersed well in liquid fluid and biocompatible than G. Therefore, incorporation of both G and GO into the biopolymer matrix was suggested for hard tissue regeneration [28]. The culture of bone marrow-derived mesenchymal stem cells on GO matrix showed an increase in cell attachment, proliferation, and differentiation into osteogenic lineage [30]. Also, GO functionalized bionanocomposite as a scaffold showed a control of dental pulp stem cell fate [31].

CNTs are allotropes of carbon with a cylindrical nanostructure made of graphene sheets rolled in on themselves to form a tube. They have unique electrical, structural, and mechanical properties, which makes them potentially useful for applications in many biomedical area [32]. In particular, the feasibility of using CNTs as a substrate for neuronal growth has been demonstrated due to their structural similarity and several groups have suggested that CNT networks or their scaffolds are able to interact with neural cells to support their growth, adhesion, and migration, which is helpful for nerve regeneration in head and neck surgery [33, 34]. As incorporated in bionanocomposites, neurons grown on CNTs incorporated bionanocomposites are more suitable than those grown on biopolymer counterpart [35]. In a previous study, CNT incorporated PLCL scaffolds improved neurite outgrowth of neural crest-derived rat pheochromocytoma cell line (PC-12) via expression of focal adhesion kinase expression [36, 37]. Another study confirmed improvement of neurite outgrowth in primarily cultured rat dorsal root ganglia (DRG) neurons [37].

Elemental silver is well known as antimicrobial agents in curative and preventive for centuries [38]. About its action against microbes, it possesses both a bactericidal impact and an oligodynamic effect. Silver nanoparticles seem to be stronger candidates compared to the silver microparticle due to enhanced surface area and ion releasing activity. Moreover, unlike pharmaceutical biomolecules which may destroy beneficial enzymes, silver nanoparticles have selectivity and leave these beneficial enzymes intact [39]. Notably, comparing to all other available antimicrobial agents, silver is considered as the most powerful antimicrobial agent that possesses a strong toxicity toward a broad range of microorganisms, and simultaneously a remarkably low human toxicity [40]. Therefore, intensified interest in bionanocomposites with silver nanoparticles is given due to the high antimicrobial effect of silver nanoparticle as well as the unique characteristics of biopolymers [41]. Biomedical applications of biopolymer/silver nanoparticle composites showed antibacterial effect against Gram-negative and Gram-positive bacteria including streptococcus mutans and porphyromonas gingivalis which are cause of failure of dentin and PDL regeneration [42, 43].

To provide additional functionality, a range of nanoparticles can be incorporated within the biopolymeric network to fabricate bionanocomposites. Most nanomaterials can be divided into four different categories: zero-, one-, two-, and three-dimensional nanomaterials. Zero-dimensional (0D) nanomaterials are atomic clusters mostly composed of metallic elements such as silver and gold. One-dimensional (1D) nanomaterials include metal nanorods, carbon nanotubes, and ceramic crystals. Most two-dimensional (2D) nanomaterials have included layered structures such as graphene oxide sheets and silicate nanoplatelets, whereas three-dimensional (3D) nanomaterials include spheroidal bioactive glass nanoparticles, dendrimers, and other spherical particles. Due to the difference in surface to volume ratio, these nanomaterials interact with biopolymers via substantially different mechanisms and result in unique biological property combinations compared with their nanocounterparts. The dimensionality of incorporated nanomaterials will stimulate specific cellular pathways via multiple channels, providing investigators with a host of tools for controlling cell behavior. Thus, the type of nanomaterials used to make a bionanocomposites majorly plays a role in determining the end application of these biomaterials. Bionanocomposites take a variety of forms for applications in dentistry.

3. Application

3.1. Dentin-Pulp Complex Regeneration. Dentin-pulp complex consists of mineralized hard tissue present in the crown or root of teeth and underlying fibrous pulp tissue. The dentin is made up of carbonate-rich calcium deficient hydroxyapatite, type I collagen, and dentinal fluid, which is similar to blood plasma [44]. Dentin is produced by odontoblasts and it acts to protect the underlying pulp tissue and support the enamel or cementum. Dentin is analogous to bone in terms of composition and hierarchical structure while it lacks the ability to remodel. However, it responds to injury by forming a reactive or tertiary dentin to protect the underlying pulp tissue [45]. Therefore, regeneration of dentin-pulp complex is considered important issue in preservative dentistry.

Most of bionanocomposites for dentin-pulp complex regeneration have been synthesized by electrospinning or 3D printing technology along with the sol-gel technique for glass nanoparticle. Silica nanoparticles are able to be incorporated into various biopolymers due to their unique properties like high mechanical resistance, heat resistance, and chemical stability [46]. Due to the aforementioned advantages offered by silica nanoparticle, tubular bionanocomposite matrix of poly(ethyl methacrylate-co-hydroxyethyl acrylate) [P(EMA-co-HEA)] was synthesized with 0–20 wt% concentration of silica nanoparticle by a fiber-templating method so as to mimic the tubular structure of natural dentin [47–49]. Fabricated tubular structures were found to induce the precipitation of nanosized hydroxyapatite on their surface and to facilitate odontoblastic cell growth with the integration of host mineralized tissue.

Hydroxyapatite nanoparticle is a very commonly used nanomaterial in tissue engineering. This material has great biocompatibility and bioactivity. Electrospun PCL/gelatin scaffolds with hydroxyapatite nanoparticles was investigated for dentin-pulp regeneration [50]. For the in vitro evaluation, DNA content, ALP activity, and OCN measurement showed that bionanocomposites significantly increased odontoblastic differentiation activity confirmed by in vitro ALP activity and in vivo OCN, BSP, DSPP, and DMP-1 expression while sustaining adhesion and proliferation of hDPSCs.

Halloysite is a natural nanosized tubular aluminosilicate clay mineral that can store and release molecules in a controllable manner with biocompatibility. An electrospun bionanocomposite scaffold composed of polydioxanone was designed and fabricated with 0.5–10 wt% halloysite nanotubes incorporation. This scaffolds supported the attachment and proliferation of hDPSCs. Results of quantitative proliferation assay indicated high level of biocompatibility, rendering them good candidates for the potential encapsulation of distinct bioactive molecules [51].

With the development of nanotechnology, bioactive glass nanoparticles have been applied for pulp-dentin tissue complex regeneration in dentistry over hydroxyapatite nanoparticles. Bioactive glass nanoparticles offer better biological and mechanical properties for substrate biopolymer per weight of particle, as compared with microsized counterparts and biopolymer [52]. Bionanocomposites incorporating collagen 3D matrix and bioactive glass nanoparticle were produced by an electrospinning method as a scaffolding matrix for dentin-pulp regeneration [53]. The involvement of bioactive glass nanoparticles within the fibrous collagen matrix significantly enhanced human dental pulp stem cells (hDPSCs) growth and differentiation into odontoblasts, as confirmed by the cell viability assay, alkaline phosphatase (ALP) activity, mineralization test, and the mRNA levels of odontoblastic genes such as ALP, osteocalcin (OCN), osteopontin (OPN), dentin sialophosphoprotein (DSPP), and dentin matrix protein-1 (DMP-1). Moreover, gene expression of integrin $\alpha 2\beta 1$ in hDPSCs responsible for binding to collagen molecular sequence was highly stimulated, suggesting that pulp and dentin regeneration were related to the adhesion molecule-receptor mediated process. Based on this work, collagen-bioactive glass nanoparticle bionanocomposite was able to be potentially useful for culture of hDPSCs and their odontogenesis in the dental pulp tissue regeneration.

Similarly, nanofibrous matrix made of polycaprolactone-gelatin and bioactive glass nanoparticles was fabricated to investigate the effects of odontogenic differentiation of hDPSCs by an ALP activity assay, calcified nodule formation, and odontogenic related mRNA expression [54]. Although cell growth and attachment on the bionanocomposites were similar to those on biopolymer counterpart, ALP activity, mineralized nodule formation, and mRNA, expressions involving ALP, OCN, DPN, DSPP, and DMP-1 were greater on bionanocomposites. They also upregulated adhesion receptors such as integrin $\alpha 1$, $\alpha 2$, $\alpha 5$, and $\beta 1$, integrin downstream pathway, bone morphogenetic protein (BMP), and mitogen-activated protein kinases signaling pathway. Therefore, PCL-gelatin based bionanocomposites incorporated bioactive glass nanoparticle is considered to be promising scaffolds for dental tissue regeneration.

3.2. Periodontal and Alveolar Bone Regeneration. Periodontium consists of the alveolar bone, gingiva (gum), cementum, and periodontal ligament. Alveolar bone and cementum are the mineralized or hard tissues whereas the gingiva and PDL are the fibrous or soft tissues. Particularly, cementum and PDL are the only tissue in periodontium, which serve as anchoring complex to link between root of tooth and surrounding alveolar bone, which plays a role in protecting amounts of alveolar bone from pathogens in oral environment. Cementum is an avascular, noninnervated calcified tissue that binds to dentin of the root and has major cells for producing PDL: cementoblast. Due to the complexity of structure, intimate relationship, and protection function of cementum-PDL complex, regeneration of periodontal tissue could be major hurdle to overcome in dentistry. Although guided bone and tissue regeneration membranes are currently in use for periodontal regeneration, they have certain drawbacks such as weak mechanical properties, poor cementum-PDL complex regeneration capacity, and increase of infection risk. To overcome the current disadvantages, bionanocomposites may serve as a suitable matrix for the attachment and proliferation of cementoblasts as well as osteoblasts and fibroblasts. Scaffolds can be developed from natural or synthetic biopolymers. But these scaffold matrices may lack adequate mechanical and osteoconductive properties. Bionanocomposites offer various advantages in comparison to bulk materials such as high surface area to volume ratio, close contact to surrounding tissues, enhanced biocompatibility, osteoconductivity, cell attachment, and proliferation.

Alginate is a natural polysaccharide extracted from brown seaweeds. Chemically, alginate is a linear polymeric acid composed of 1,4-linked β-D-manuronic acid and α-L-guluronic acid residues, which is highly hydrophilic, biocompatible, biodegradable, relatively economical, and widely utilized in biomedical application. Bioactive glass nanoparticle-incorporated alginate composite scaffold was fabricated and characterized in terms of mechanical and biological properties such as swelling ability, in vitro degradation, biomineralization, and cytocompatibility [55]. The results indicated enhanced biomineralization and protein adsorption while they have reduced swelling and degradation. In addition, adhesion and proliferation of human periodontal ligament fibroblast were enhanced on the alginate/bioactive glass nanoparticle composite matrix in comparison to the control alginate scaffolds. The presence of bioactive glass nanoparticles enhanced the ALP activity of the human periodontal ligament fibroblast cells cultured on the bionanocomposite scaffolds.

Gelatin, one of the popular nature biopolymers for biomedical application, has many advantages such as its cell-adhesive structure, low cost, off-the-shelf availability, high biocompatibility, biodegradability, and low immunogenicity [56]. Hydroxyapatite nanoparticle-incorporated gelatin bionanocomposites have been prepared for studying periodontal tissue engineering scaffolds [57]. They prepared two different scaffolds 2.5% gel/2.5% HA and 2.5% gel/5% HA and showed increased cell attachment and proliferation of periodontal ligament (PDL) fibroblast cells.

Chitosan is obtained by alkaline deacetylation of chitin and presents excellent biological properties, such as biodegradability, biocompatibility, and immunogenicity, as well as antibacterial, antifungal, and wound-healing activity. Its degradation products are nontoxic, nonantigenic, nonimmunogenic, and noncarcinogenic. Chitosan also evokes minimal foreign body reaction. The positive surface charge of this material and its biocompatibility enable it to effectively support cell growth, attachment, and differentiation. When placed in hydrated environments, chitosan turns into a flexible material, which is an advantage over more rigid synthetic materials like PLA and polyglycolic acid (PGA). Therefore, combination of chitosan with bioactive glass nanoparticles in order to produce a novel guided tissue regenerative membrane was fabricated for periodontium regeneration [58]. The addition of bioactive glass nanoparticles to chitosan membranes improved bioactivity while it decreased the mechanical potential. These bionanocomposite membranes promoted human periodontal ligament cells metabolic activity and mineralization. The results indicate the potential use for temporary guided tissue regeneration membrane in periodontal regeneration, with the possibility to induce bone regeneration.

3.3. Enamel Substitute. Bionanocomposites, called dental resin nanocomposites, are recently used for substitutional materials for enamel and dentin structure in tooth over conventional resin composites. As most commercial dental composites, there is a Bis-GMA monomer consisting of organic matrix and other base monomers such as triethylene glycol dimethacrylate (TEGDMA), urethane dimethacrylate (UDMA), ethoxylated bisphenol-A-dimethacrylate (Bis-EMA), decanediol dimethacrylate (D3MA), bis(methacryloyloxymethyl) tricyclodecane, and urethane tetramethacrylate (UTMA) [5]. To overcome the lack of mechanical properties and polymerizing shrinkage, modern dental resin composite systems contain fillers such as quartz, colloidal silica, and silica glass containing barium, strontium, and zirconium. These fillers increase strength and modulus of elasticity and reduce polymerization shrinkage, the coefficient of thermal expansion, and water absorption. Along with the nanotechnology development, nanoparticles were introduced in dental resin composites due to the high loading capability and ion releasing potential.

For increasing the mineral content of the tooth, enhancing mechanical properties of composites and reducing polymerization shrinkage in polymerized composites, bionanocomposites were developed with nanoparticles or nanofibers as reinforcement. Dental resin nanocomposites consist of a photopolymerizable organic resin matrix and silane-treated inorganic nanofillers. Nanofillers are added and distributed in a dispersed form or as clusters. There are several products of nanocomposites on the market. They have 57~70 vol% (76~84 wt%) of nanofiller and most of the nanofillers consist of silica nanoparticles from 10 nm to 75 nm. These nanoparticles that are well-dispersed in the polymer matrix on a nanoscale level allow for increased filler loading and reduced viscosity of bionanocomposites and thus result in increased mechanical properties such as hardness, abrasion resistance and fracture resistance, and polishability and in reduced polymerization shrinkage into 1.4%–1.6% by volume and consequent shrinkage stress [59]. As the particle dimension in resin matrix decreases, the load-bearing stress on the resin is reduced, which inhibits crack formation and propagation [60]. To increase mineral content to control dental caries, calcium, phosphate, or fluoride ion releasing nanofillers have been developed, such as nanoparticles of dicalcium phosphate anhydrous- (DCPA-) whiskers, tetracalcium phosphate- (TTCP: $Ca_4(PO_4)_2O$-) whiskers, kaolinite ($Al_2Si_2O_5(OH)_4$), and calcium fluoride. Previous studies showed that when Ca and PO_4 ions were released from the bionanocomposites, they reprecipitated to form hydroxyapatite on the surface of bionanocomposites or inside the tooth lesion, significantly increasing the mineral content of the lesion [61]. Increasing the DCPA or TTCP particle surface area by decreasing each particle size to nanoscale significantly increased the Ca and PO_4 release, and bionanocomposites with the nano-DCPA or nano-TTCP exhibited the highest release [62]. In addition, when the pH was reduced from neutral to acidic condition, increased Ca and PO_4 ions are released by about sixfold, which may have the potential to provide caries-inhibiting capability [62].

Fluoride release from restorative materials is considered to inhibit tooth demineralization and caries development and also to strengthen the neighboring enamel or dentin. Xu et al. added calcium fluoride nanoparticles (~56 nm) up to 30% to bionanocomposites and found that the fluoride release was better detected compared to traditional resin counterpart while strength and elastic modulus of the nanocomposite are sustained [63, 64]. Because of unique structural of kaolinite, which has high surface area for adsorption of fluoride, kaolinite is considered as an excellent carrier compared with the conventional silica nanoparticle used in conventional composite resins [65]. These polymer-kaolinite bionanocomposites have the potential to provide sustained release of fluoride due to strong adsorption of kaolinite to fluoride during the fabrication process.

4. Conclusion

Organic-inorganic bionanocomposites have shown a good mechanical flexibility in dental applications. Inorganic materials play a key role in sustaining and supplementing mechanical properties of polymer matrices and in further favoring cellular behaviors. As a result, in dentistry, bionanocomposites are able to be substituted for native tissue as shown in many clinical cases. Of inorganic materials, for example, bioactive glass nanoparticles or MNPs have shown excellent biological activity in relation with bone-derived cells and tooth-derived cells, such as odontoblasts and dental pulp stem cells for bone or dentin-pulp complex regeneration. Highly stiff G and GO materials and CNTs have shown a good affinity to cells or biomolecules and so far have been used as a substrate for neuronal growth due to their structural similarity and its affinity to neural cells. Elemental silver can be also incorporated as antimicrobial agent. Along with above nanoparticulates, bionanocomposites consisting of halloysite, silica, hydroxyapatite nanoparticle, and so on have been developed for dentin-pulp complex, periodontal and alveolar bone regeneration, or enamel substitute. However, most bionanocomposites still lack the data for clinical applications when compared to data of monophasic resin. Further in vivo or clinical studies are imperatively needed for use of bionanocomposites in dental applications.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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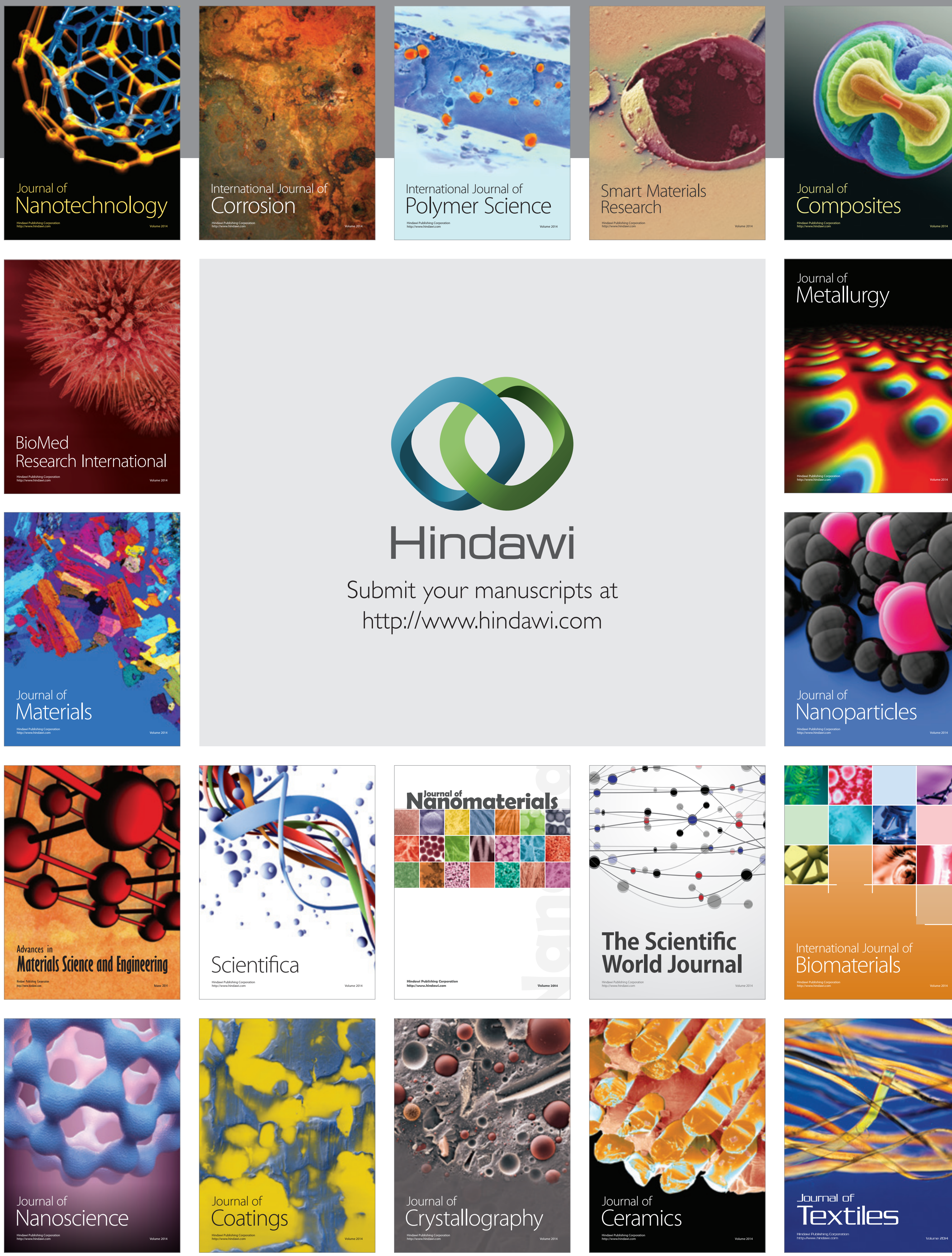
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