Graphene Derivatives in Caries Management

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Graphene is a two-dimensional mono-atomic sp2 hybridized carbon-based nanomaterial known as the thinnest and strongest element in existence. Dental caries is the chronic local damage of dental hard tissue (enamel, dentin, and cementum) that acidic byproducts of bacterial metabolism of dietary carbohydrates often cause, and periodontal disease is the inflammation of periodontium (gums, periodontal ligaments, and alveolar bone surrounding the teeth); both are associated with microbes.

Keywords: caries ; remineralization ; graphene ; periodontal

1. Introduction

Graphene is a two-dimensional mono-atomic sp2 hybridized carbon-based nanomaterial known as the thinnest and strongest element in existence [1]. Of all the generic compounds and nanomaterials used in antimicrobial and regenerative research, graphene and its derivatives have attracted the attention of researchers in recent decades. It has a high surface area, excellent electrical and thermal conductivity, mechanical properties, low coefficient of thermal diffusion, and a significantly high aspect ratio. These features make it outstanding in a number of potential applications in a variety of fields, from engineering to biology [2][3][4][5][6][7][8]. Graphene and its derivatives can act as good substrates for diffusion, dispersion, and stability of many antimicrobial nanoparticles (i.e., copper, silver, iron, magnesium, calcium, titanium dioxide, zinc oxide, etc.) [9][10][11][12][13][14][15]. Moreover, graphene and its derivatives are suitable candidates for biological/chemical functionalization [16][17]. Their biocompatibility received great attention in the research on their potential applications in the biological, biomedical, medical, and dental fields [18]. Dentistry has a broader aspect in preventing and restoring decayed or lost teeth and dental tissues. Graphene's potential antibacterial and tissue regenerative properties were widely used in various dental research fields [19][20][21]. Graphene is especially used in caries and periodontal disease management using its antibacterial properties, dental hard and soft tissue remineralization capacities, regeneration abilities, as well as its periodontal tissue and bone regeneration properties [20].

Dental caries is the chronic local damage of dental hard tissue (enamel, dentin, and cementum) that acidic byproducts of bacterial metabolism of dietary carbohydrates often cause [22], and periodontal disease is the inflammation of periodontium (gums, periodontal ligaments, and alveolar bone surrounding the teeth) [23]; both are associated with microbes. Generally, there is a balance between microfloral and microbial colonization and the oral microenvironment [24]. Unpleasant consequences occur when this balance is disturbed. The main cariogenic microbe is *Streptococcus mutans*, which generates organic acids, thus reducing the oral pH level and leading to demineralization of the dental hard tissue surface [25]. On the other hand, *Porphyromonas gingivalis* and *Fusobacterium nucleatum* are responsible for gingivitis and periodontitis, respectively [26]. Several strategies have been investigated, established, and employed in different communities and have brought beneficial implications for many world populations to manage these diseases. Preventive measures against dental caries and periodontal diseases have been remarkably improved over the last few decades with the advancement of nanotechnologies and nanomaterials. Whatever the immense struggles, a large number of the population still suffer from these diseases and eventually lose teeth [27].

Generally, humans cannot reproduce or regenerate or regrow teeth or tooth tissues. Although oral and soft tissue can be repaired, the regeneration or repair of hard tissues (enamel, dentin, and bones) is inadequate or sometimes impossible. Interestingly, in addition to biomaterials sciences, preventive and regenerative dentistry is also advancing well. Preventive and regenerative dentistry research mostly focuses on preventing dental caries and periodontal disease. Simultaneously, they are focused on restoring lost tooth tissue because of caries and or periodontal diseases. These days, the high incidence of periodontal diseases is a major concern [28]. Researchers are exploring real-time solutions for lost tooth tissue and bone, but it is a great challenge to achieve the outcome [29][30][31]. Regenerative dentistry and tissue engineering are now the most challenging research topics in this field. With these research advancements, it is not only periodontal diseases and tooth loss but also surgical resection of the maxillofacial hard and soft tissue (jawbone, tongue), due to trauma or oral cancers, that will also benefit.

Regardless of the challenges ahead, the latest advances in nanotechnology have played a biomimetic role and have shown tremendous potential in dental hard and soft tissue regeneration. Various nanomaterials are being added continuously and have produced many clinical benefits in dentistry using tissue engineering properties, which include: the advanced treatments of caries and periodontal diseases, bone regeneration, feasible biological tooth repair after caries, and is probably advancing towards regrowing entire lost teeth [32][33].

2. Graphene Derivatives in Caries Management

Dental caries is a highly prevalent disease. Cariogenic biofilms are mainly responsible for dental caries. Caries initiates with the chemical dissolution of dental hard tissue by the acid produced through dietary carbohydrate metabolism of bacteria that adhered (as biofilm) to the tooth surface. A prolonged stagnation of biofilm enhances enamel and dentin desolation and progresses to cavity formation on the tooth surface [34][35]. These biofilms are the organized colony of microbial communities enclosed in an extracellular cohesive matrix (i.e., extracellular polysaccharide) where *Streptococcus mutans* is the main cariogenic pathogen. They produce insoluble extracellular polysaccharides, which facilitate bacterial growth and the formation of cariogenic biofilms. This is why most of the research focuses on developing biomaterials to inhibit *Streptococcus mutans* [36].

Remineralization of demineralized caries also can stop caries progression. It is said that maximum mineralization in the human body is seen in teeth by continuous demineralization and remineralization throughout life with varying amounts to maintain tooth integrity [37]. It breaks if demineralization suppresses the remineralization and results in caries progression [38]. Therefore, either stopping the biofilm formation, remineralization of demineralized hard tissue, or a combination of both is the scientifically logical point of view for caries prevention.

Although caries risk assessment and remineralization of initial lesions have controversy, diverse advanced research and nanotechnology have developed risk-specific biomaterials or board functional nano-biomaterials and opened the doors to caries prevention [39]. Graphene's antibacterial effect became known first in 2010 and was widely explored afterward for various applications [20][40]. Currently, graphene has attracted much attention in caries research as a preventive, cariostatic, and remineralizing material. Research has well demonstrated that graphene derivatives are significant in inhibiting cariogenic bacteria, preventing dental hard tissue demineralization, and facilitating remineralization.

2.1. Application against Cariogenic Pathogens

Although graphene and its derivatives can inhibit cariogenic bacteria, most of them are studied together with antimicrobial metals or non-metal or polymer nanoparticles, such as copper, silver, zinc, peptides, and polymer nanoparticles, to improve the antibacterial properties or facilitate the sustainable release of incorporated nanoparticles [41][42][43][44][45][46][47][48][49][50][51][52][53][54][55]. They are also studied with existing dental materials, especially incorporated into restorative cements, either to improve antibacterial properties against *Streptococcus mutans*, reduce dental hard tissue demineralization, or facilitate remineralization [44][47][48][50][56][57][58].

Graphene nanosheet was reported as very effective against *Streptococcus mutans* [47]. Simultaneously, graphene oxide nanosheets were demonstrated effective in reducing *Streptococcus mutans* [44][45]. Subsequently, metal functionalized graphene materials, graphene-silver nanoparticles, were also found effective against *Streptococcus mutans* without any significant cytotoxicity [13][41][48][49]. Similarly, reduced graphene-silver nanoparticles and graphene-nanoplatelets doped silver nanoparticles showed an antibiofilm effect against *Streptococcus mutans* biofilm [42]. Moreover, graphene oxide-copper nanocomposites reduced *Streptococcus mutans* growth significantly [46]. In addition, graphene-zinc nanocomposites were effective in reducing *Streptococcus mutans* biofilm. There are also reports of suppressing acid production and glucan formation, which are responsible for caries and biofilm formation [43].

In other studies, amino-functionalized graphene oxide was reported with potential against cariogenic bacteria *Streptococcus mutans* [51][54]. At the same time, graphene oxide-coated zirconia was also reported to inhibit *Streptococcus mutans* [53]. Some other studies reported that poly methyl methacrylate incorporated graphene oxide can greatly inhibit *Streptococcus mutans* growth [56][58]. Another reported that fluorinated graphene also can inhibit *Staphylococcus aureus* and *Streptococcus mutans* [57]. Some other studies reported that after treating with graphene oxide, graphene oxide-carnosine, and graphene oxide-carnosine-hydroxyapatite the survival rate of *Streptococcus mutans* was significantly reduced [13][59].

Although graphene oxide and antisense vicR could significantly inhibit biofilm and extracellular polysaccharide production alone, graphene oxide–polyethyleneimine–antisense vicR was reported as superior in inhibiting extracellular polysaccharide regulation, virulence-associated gene expression, and biofilm formation. Therefore, the study suggested that graphene oxide–polyethyleneimine–antisense vicR ribonucleic acid could be a highly potent agent for caries prevention [60]. On the other hand, one study reported that graphene oxide could be a potential nanocarrier. It was described that the functionalization of graphene oxide with antimicrobial photodynamic therapy can significantly enhance indocyanine green loading and stability, and could enhance the inhibitory effects against *Streptococcus mutans* [59]. Interestingly, peptide-functionalized reduced graphene oxide nanocomposite was also reported to inhibit cariogenic bacteria [52].

By overseeing all these studies, it can be hypothesized that either pristine or functional nanocomposites of graphene and its derivatives could potentially be used against cariogenic bacteria. However, the established mechanism of antibacterial activities of graphene derivatives is still to be explored. Several antibacterial mechanisms have been described to demonstrate graphene and its derivatives in inhibiting cariogenic microbe and their biofilm. Physical damage, membrane stress, oxidative stress, and electron transfer were well considered [61]. Therefore, advanced studies should be performed to translate the standard anticaries mechanism of graphene derivatives for caries management in clinical settings.

2.2. Application for Tooth Remineralization

As a consequence of the *Streptococcus mutans* acidic by-product, demineralization initiates dental caries. At the same time, the counteraction of remineralization protects teeth from decay. Graphene can facilitate remineralization. In a study, graphene-fluorine was reported to enhance the remineralization of white spot lesions [62]. At the same time, graphene oxide fluorhydroxyapatite was also reported to prevent demineralization by resisting hydroxide dissolution [63].

In several studies, graphene oxide conjugated bioactive glass was reported to significantly increase the anti-demineralization effect, microhardness, shear bond strength, and adhesive remnant index with no or low cytotoxicity [13][64]. Graphene oxide and montmorillonite were reported to exhibit enhanced mechanical properties and bioactivity while incorporated in resin-based composite [65]. Interestingly, multi-walled carbon nanotube/graphene oxide hybrid carbon-based nanohydroxyapatite was reported to protect against dentin erosion [66].

In one study, reduced graphene oxide-silver was found to reduce enamel surface roughness and mineral loss, thus reducing the lesion depth [67]. Moreover, another study showed that graphene oxide could be a bioceramic support material to enhance hydroxyapatite deposition [68]. In addition, graphene oxide quantum dot incorporated mesoporous bioactive glass was reported to show excellent dentinal sealing and rapid mineralization. They promoted hydroxyapatite formation without interfering with calcium, silicon, and phosphate ions release [69]. Although there are potentials and limitations of graphene and its derivatives on antimicrobial effect, remineralization, and dual action there is no strong clinical evidence; therefore, advanced investigations are required to validate the optimal outcome and clinical applications.

Table 1 shows the investigated results and potential applications of graphene materials in caries management. The antimicrobial activity, remineralization, or dual action excels graphene and its derivatives to be potential candidates in advanced caries research. In the future, advanced translational research will be evidence to translate graphene materials into clinical applications.

Table 1. The properties of graphene and its derivatives for the management of dental caries.

Graphene and Its Derivatives	***Properties [Reference(s)]***
Graphene	
Graphene	**Inhibits cariogenic biofilm [47][50]**
Graphene-silver nanoparticles	**Inhibits cariogenic biofilm [42]**
Graphene-zinc nanoparticles	**Inhibits cariogenic biofilm [43]**
Graphene-zinc oxide nanoparticles	**Inhibits cariogenic biofilm [70]**
Graphene-fluorine	**Inhibits cariogenic biofilm [57][62]** **Promotes enamel and dentin mineralization [62]**
Graphene Oxide	

Graphene and Its Derivatives	*Properties [Reference(s)]*
Graphene oxide	**Inhibits cariogenic bacteria [13][44][45][51][53][54] and fungi [71]** **Inhibits cariogenic biofilm [53][60][72][73]** **Promotes enamel and dentin mineralization [63][65][66][68]**
Graphene oxide-silver nanoparticles	**Inhibits cariogenic bacteria [13][41][48][49]**
Graphene oxide-bioactive glass	**Inhibits cariogenic bacteria [64]** **Promotes enamel and dentin mineralization [64]**
Graphene oxide-silver-calcium fluoride	**Inhibits cariogenic bacteria [13]**
Graphene oxide-carnosine-hydroxyapatite	**Inhibits cariogenic bacteria [59]**
Graphene oxide-copper	**Inhibits cariogenic biofilm [46]**
Graphene oxide-polyethyleneimine	**Promotes enamel and dentin mineralization [74]**
Graphene oxide-poly-methyl methacrylate	**Inhibits cariogenic bacteria [56][58]**
Graphene oxide-nanoribbon	**Inhibits cariogenic biofilm [55]**
Reduced Graphene Oxide	
Reduced graphene oxide	**Inhibits cariogenic bacteria [52]**
Reduced graphene oxide-silver nanoparticles	**Inhibits cariogenic biofilm [48]** **Promotes enamel and dentin mineralization [67]**
Graphene Oxide Quantum Dots	
Graphene oxide quantum dots-bioactive glass	**Promotes enamel and dentin mineralization [69]**

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