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Grapheme: An Asset or a Black Box to Dentistry: A Review

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ABSTRACT

Graphene is 2-D carbon-based material exhibiting remarkable mechanical, chemical, and biological properties. Graphene and its derivates like graphene oxide, reduced graphene oxide, fluoridated graphene has been shown to influence the differentiation of stem cells and to improve properties of biomaterials. Moreover, it can be functionalized and combined with several biomolecules, holding enormous potential to be used as drug substrates and scaffolds for cell-based tissue engineering strategies also. Here in this review, we will be discussing the properties and applications of Graphene and its derivatives in dentistry.

Abbreviations: GFN: Graphene Family Nanomaterials; FLG: Few-layer Graphene; GO: Graphene Oxide; rGO: Reduced Graphene Oxide; GNS: Graphene Nanosheets

INTRODUCTION

With the advancement of biomaterials and their derivatives, graphene has bagged a lot of concentration. It is a two-dimensional carbon allotrope which has sp2-bonded carbon atoms arranged in a sheetlike arrangement forming a honeycomb pattern [1]. This arrangement lends extremely high mechanical strength and modulus of elasticity. Its remarkable structural, chemical, thermal, and biological properties have been demonstrated by various researchers and can be applied in dentistry [1,2]. Moreover, graphene presents with unparallel electronic properties and offers a large surface area that can be chemically functionalized.

Graphene family nanomaterials (GFNs) includes ultrathin graphite, few-layer graphene (FLG), graphene oxide (GO; from monolayer to few layers), reduced graphene oxide (rGO), and graphene nanosheets (GNS) [3]. These differ from each other in terms of surface properties, number of layers, and size [4]. Among all the members of graphene family nanomaterial, GO is one of the most important chemical graphene derivatives which could be produced through energetic oxidation of graphite through Hummer's method using oxidative agents. GO possessed a variety of chemically reactive functional groups on its surface, which facilitate connection with various materials including polymers, biomolecules, DNA, and proteins [5]. rGO can be obtained by chemically, thermally, or electrochemically reducing graphene oxide, which possesses heterogeneous electron-transfer properties [6]. FG is an uprising member in the graphene family. FG has favorable biocompatibility, exhibiting a neuro-inductive effect via spontaneous cell polarization and enhancing adhesion and proliferation of mesenchymal cells providing scaffold for their growth. However, because of its properties especially antibacterial properties and tissue regenerative capacities, it has been widely reviewed and studied in medicine field considering limited in vivo and in vitro studies in dentistry. Therefore, this article reviews the recent achievements and provides a comprehensive literature review on the potential applications of graphene that could be translated into clinical reality in dentistry.

Historical review

In early 1900- Graphite oxide was prepared by Hummers, Brodie et al.

In 1962- Reduced graphene oxide (rGO) was prepared by thermal and chemical reduction of graphite oxide.

In 1970- Boehm et al. described graphene as a single layer of graphite- like carbon. Monolayer graphite was prepared by segregating carbon on the surface of nickel.

In 1999- Multiple layer graphene was isolated via micromechanical exfoliation by Rouff et al.

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In 2004- Single layer of graphene were isolated by Geim & Novoselov via mechanical exfoliation.

In 2010- A noble price was awarded to Geim & Novoselov for their contribution.

PROPERTIES OF GRAPHENE AND ITS DERIVATIVES

Biocompatibility

It is essential to understand interaction of any biomaterial and its derivatives with living system. Cytotoxicity of certain material depend upon various factors like morphology (size, shape, and sharp edges), surface charge, surface functionalization, dispensability, state of aggregation, number of layers, purity, and methods of synthesis [7].

Via various in- vitro and in vivo studies scientists concluded that the concentration of Graphene oxide is directly proportional to its toxicity; 50ug/ml might be a toxicity threshold for normal mammalian cells.

Many studies suggested that Oxidative Stress is the main cause, as the elevated ROS level may oxidize various molecules including DNA, lipids, and proteins inducing apoptosis or necrosis [8]. However, studies on the cytotoxicity of GFNs in oral setting are very limited.

Antibacterial Properties

Antibacterial property of graphene oxide is based on Physical damage and chemical effect.

Three main physical antimicrobial activities have been reported:

(i) GO sheets sharp edges can physically interfere with a microorganism by cutting bacteria membranes (nano-knife or nano-blade effect) [9].

(ii) GO can induce oxidative stress [10].

(iii) GO can wrap and isolate microorganisms from the environment so that they cannot find nutrition, stopping proliferation [6].

Chemical effect is primary Oxidative Stress mediated with production of Reactive Oxidative Species (ROS). Intracellular ROS accumulation causes intracellular protein inactivation, lipid peroxidation, and dysfunction of the mitochondria, which ultimately lead to gradual disintegration of cell membrane and eventual cell death [11].

Regenerative properties

Among derivatives of graphene, GO, possesses many functional groups, and has outstanding surface activities which can exert adsorptive capability to drugs, growth factors, and other biomolecules [12]. Several in vitro experiments have demonstrated that GO upregulates *β*-catenin protein expression and activate catenin/Wnt signaling pathway, increasing the extent of proliferation and differentiation of cultured cells, leading to acceleration of bone formation [13].

POTENTIAL APPLICATIONS IN DENTISTRY

Periodontology

Various researchers have evaluated the antibacterial activity of GO nanosheets against three most common types of bacteria and found that GO nanosheets were highly effective against the growth of dental pathogens. At GO concentration of 40 µg/mL, bacterial growth of *P. gingivalis* and *F. nucleatum* were inhibited, while, at concentration of 80 µg/mL, GO absolutely killed all *S. mutans* [14].

Guided Bone Regeneration is a popular procedure in periodontic dentistry. A number of attempts had been made to modify barrier membrane have been made to improve its biocompatibility. Radunovic [15] evaluated the effect of collagen membrane coated with GO (10 µg/mL) on the viability and metabolic activity of dental mesenchymal cells. The study concluded that GO coating at induces PGE2 secretion, controls inflammation, and promotes DPSCs differentiation which is probably due to GO's large reactive surface area providing ideal platform for biofunctionalization and concentrating chemical, proteins, and growth factors for faster differentiation [16,17].

Dental Implants

After dental implantation, osteogenic properties of implant material are the most essential endeavor for osseointegration while at the soft tissue interface, preventing bacterial invasion is obligatory to ensure a tight epithelial seal [18].

When graphene is coated on titanium substrate, the hydrophobic character of graphene film exerts self-cleansing effect on its surfaces, decreasing the adhesion of microorganism including *S. sanguinis* and *S. mutans* [19,20]. Additionally, compared to titanium alone, graphene shows osteogenic property promoting the expression of osteogenic related genes RUNX2, COL-I, and ALP, boosting osteocalcin gene and protein expression, and consequently increasing the deposition of mineralized matrix [21].

Endodontics

Sharma [22] conducted an in vitro study was to evaluate the antimicrobial effectiveness of Graphene Silver Composite Nanoparticles as an endodontic irrigation solution. He concluded that the percentage reduction of E. Faecalis in Saline was 21.64 %, with Sodium hypochlorite it was 80.40% and the maximum reduction was observed in Graphene Silver Composite Nanoparticles with 86.85%. His results were in support of several studies which have shown activated carbons and graphene-based materials, can disrupt and kill bacteria via the oxidation of glutathione, an important cellular antioxidant [23,24].

With modernization in canal disinfection techniques, Photodynamic therapy is gaining attention for effective canal disinfection while preserving dentin structures. One of the most popular in this technique is nontoxic photosensor, indocyanine green (ICG), but it has poor stability and concentration-dependent aggregation [25]. Modifying ICG with GO not only significantly reduced number of *E. faecalis* and *S. mutans*, but also improved the stability and bioavailability of ICG, preventing its degradation and aggregation [25,26].

Nishida [12] conducted an in-vitro study to evaluate the effect of a GO coating on cell proliferation and differentiation. They also assessed the bioactivities of collagen scaffolds coated with different concentrations of GO and concluded that GO affects both cell proliferation and differentiation. Infact, it improved the properties of collagen scaffolds. Further tests revealed, low concentrations of GO scaffold enhances cell in-growth and is highly biodegradable, whereas high concentrations of GO coating resulted in adverse biological effects [27,28].

Biodentine and Endocem- Zr are considered the safest bioactive cements in endodontics for management of perforation, retrograde root filling, and pulp capping. But these presents with shortcomings like high pull-out bond strength, long setting time, and medium mechanical properties. Researchers have demonstrated that addition of 3 wt % graphene nanosheets, significantly decreased the setting time of both cements [29]. Also, a decrease in push out strength of Endocem-Zr was observed which requires further studies for clinical use [30].

Incorporating GO into MTA also exhibited positive influence on the workability of the cement. It enhanced the degree of hydration by increasing the nonevaporable water content and calcium hydroxide content, contributing to the refinement of pore structures, and subsequently increasing the compressive strengths and suppressing crack propagation in the matrix at nanoscale. Introduction of 0.03% by weight GO into cement paste can increase their compressive strength and tensile strength by more than 40% [31,32].

Conservative Dentistry

Manduo [33] conducted an in-vitro study and showed that, GO showed excellent antibacterial effect on *S. mutants* in both planktonic and biofilm forms in a concentration-dependent manner. The most accepted mechanisms for the antibacterial activities of graphene materials are the physical disruption of cell membranes [34], oxidative stress damage and trapping or wrapping in addition, GO nanosheets with more oxygen containing functional groups exerted higher toxicity at low concentrations (80 g/mL), indicating that the functional groups played a dominant role in the antibacterial outcome.

GIC is the most popular restorative material used but presents with certain physical limitations. In recent years, attempts had been made to incorporate graphene nanomaterial into commercially available glass ionomer. Graphene, when combined with glass ionomer, has significantly enhanced physio-mechanical properties of GIs [35]. Fluoride graphene with glass ionomer could produce a GICs/FG composites matrix, which could significantly enhance the mechanical, tribological, and antibacterial properties of glass ionomer [36].

With increased of FG content in glass ionomer, there is a decrease of pores and microcracks in the internal structure of material. An increase in antibacterial ability was also seen making it less susceptible to erosion, disintegration and microbial invasion [37].

CONCLUSION

Graphene has been trending as a new material in dentistry recent times. Some researchers are conducting studies using graphene and its derivatives as a new product, while some are modifying it to incorporate in conventional dental materials. In both situations' graphene has been shining, due to its good physical and mechanical properties. Graphene and its derivatives are holding an enormous potential application to dentistry, but still no in-human studies have been conducted to evaluate its performance in oral environment, which is itself a complex niche.

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