

## Graphene Oxide: The Promising Potential in Dentistry: A Review

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### ABSTRACT

**Objectives:** In recent years the applications of graphene oxide (GO) have been extensively studied in various fields of medicine, due to its antibacterial properties and the ability to regenerate tissues. In dentistry, graphene oxide (GO) is also used to complement existing materials due to its unique properties, however, research on the use of graphene in dentistry is limited. What dictates a comprehensive review of the literature on the prospects for the use of graphene in clinical dentistry. In this review, we aim to highlight the potential of Graphene oxide, current understanding, and knowledge gaps regarding the antimicrobial behavior and biocompatibility of this materials. The purpose of this review article is to provide an overview of the use of graphene oxide (GO) in dentistry. **Methods:** Bibliographic databases PubMed, Embase, and Scopus were surveyed. The review focuses on the areas of application of Graphene oxide (GO) in dentistry, mainly based on a review of the most cited scientific papers in international peer-reviewed journals. **Results:** Graphene oxide (GO) has a unique structure and properties that differentiate it from other materials. Scope of application Graphene oxide (GO) broad in dentistry, it is used in prosthetics and restorative dentistry to optimize polymers and adhesives, dental implantology, to modify the surface of dental implants, to optimize the osteogenic properties of engineered tissue scaffolds through both surface and composite modifications, in periododontology and in endodontics thanks to his antimicrobial behavior. **Conclusion:** From this review, it can be concluded about the prospects for future developments, the use of Graphene in dentistry. Graphene oxide (GO) has the potential for future clinical applications in a variety of dental applications.

**Keywords:** Nanomaterials, biocompatibility dental materials, Graphene oxide.

## INTRODUCTION

Dental materials placed in the oral cavity must be non-cytotoxic and biocompatible, resistant to mechanical stress. There is a strong trend towards the continuous development of dental materials with improved properties. In the 21st century, nanotechnology plays an important role in almost all areas of science, technology, medicine, including dentistry. Nanotechnology is the art of creating a variety of materials with different properties and functions, which opens up great prospects in the field of dental materials science. Nanotechnology is usually referred to as technology leading to the production of materials of nanometer size (10<sup>-9</sup> microns). Nanostructures contain nanoparticles of different sizes (zero-, one-, two- and three-dimensional). New materials based on nanomaterials have improved physicochemical and mechanical properties in combination, which makes them excellent materials for some dental procedures. The use of nanotechnology in dentistry is wide and includes nanorobotics, nanodiagnostics, nanomaterials, and thanks to these achievements, many dental problems are solved for the better - from the diagnosis of dental diseases to more effective treatment methods. It is clear that current developments in nanotechnology hold promising prospects for all aspects of dentistry. This review presents a perspective advantage Graphene oxide (GO) in dentistry. All the data and articles putted in this review are gathered from Google Scholar, PubMed, and some dental databases. The use of Graphene oxide in dentistry is enormous and includes prosthetics, endodontics, conservative and aesthetic dentistry, periodontics, implantology, and regenerative dentistry. Physical and technological properties Graphene Oxide (GO) Graphene oxide (GO) family nanomaterials was first obtained by Geim and Novoselov in 2004 [1,2]. Graphene oxide (GO) include ultrathin graphite, multilayer graphene (FLG), graphene oxide (GO; monolayer to multiple layers), reduced graphene oxide (rGO), and graphene nanosheets (GNS). GO is one of the crystalline forms of carbon, which is a single monolayer of sp<sup>2</sup> hybridized orbitals in a tightly packed to a two-dimensional (2D) honeycomb lattice, each carbon atom has three  $\sigma$ -bonds and an out-of-plane  $\pi$ -bond that can bind with neighboring atoms [1]. The structure of GO consists of a single atom layer and functional groups such as carboxylic acid, epoxide, and hydroxyl groups which could make it amphiphilic [3]. GO can be produced by various approaches including chemical vapor deposition [4], mechanical cleavage of graphite, and electrochemical exfoliation of graphite [5]. GO can be further wrapped up to form zero-dimension (0D) nanomaterial like fullerenes, or rolled into nanotube (one dimension, 1D), or manipulated into 3D graphite [6]. GO sheets exist in bi-layers and multi-layers (<10), each possessing unique properties. Further increasing the number of layers significantly changes the properties of the material as a graphene stack with 10 layers behave more like graphite [6], demonstrating that the interlayer structure and coupling between the layers determine key physical properties [7].

For instance, the stacking order, relative twist, and interlayer spacing govern the electronic, optical, and mechanical properties of multi-layered graphene [8]. Additionally, graphene is a free-standing two-dimensionally active carbon allotrope, where each carbon atom in the 2D crystal is bonded to the three other adjacent carbon atoms forming a hexagonal aromatic structure [8]. This specific structure and its periodicity result in unique electrical and mechanical characteristics. The electron confinement in the orbitals are localized to neighboring carbon atoms to create the covalent  $\sigma$ -bonds [9]. Graphene's unique physical properties include hardness higher than diamond, elastic modulus as high as 1 TPa [10], thermal conductivity almost 13 times higher than copper [11], and good optical transparency with ~97.7% transmittance [12].

GO has many unique physicochemical and biological properties [13]. Graphene can be easily functionalized with bioactive compounds such as proteins, enzymes, drugs, growth factors, and DNA via physical interaction [14].

GO is highly biocompatible, can promote cell adhesion and proliferation, and can induce directed stem cell differentiation [15,16].

Since there are several types of microorganisms in the oral cavity that cause caries and periodontitis procedures in the oral cavity using dental materials are susceptible to the action of microbes, therefore it is advisable to provide dental materials with antimicrobial properties.

### **ANTIBACTERIAL PROPERTIES GRAPHENE OXIDE (GO)**

In the oral cavity, bacteria involved in caries formation are *Streptococcus mutans*, and bacteria associated with periodontitis and root canal infections are *Porphyromonas gingivalis* and *Fusobacterium nucleatum*.

GO in combination with other compounds, for example, the graphene / zinc oxide nanocomposite, exhibits enhanced synergistic antimicrobial, antibiotic-film, and antiadhesive activity against oral pathogens.

GO has been shown to have excellent antibacterial properties through a variety of mechanisms [17,18].

Researchers have identified the basic mechanisms of the antimicrobial activity of Graphene which includes physical and chemical effects.

Physical mechanism GO's antimicrobial effect is caused by the fact that graphene materials penetrate the cell membrane of microbes, causing leakage of intracellular substance, leading to cell death. The chemical antimicrobial effect of Graphene is caused by primary oxidative stress mediated by ROS production. Excessive accumulation of intracellular ROS causes inactivation of intracellular protein, lipid peroxidation and mitochondrial dysfunction, which in turn leads to the gradual destruction of the cell membrane and, ultimately, cell death [19].

Lee et al. have created PMMA, including nano-sized graphene oxide (nGO), which has shown antiadhesive effects against microbial species (*C. albicans*, *E. coli*, *S. aureus* and *S. mutans*) in artificial saliva. They observed a persistent antimicrobial adhesive effect for up to 28 days [20].

Majority of studies find GO as most effective by damaging the microbial cells with mechanical interaction of sharp edges as well as by the generating reactive oxygen species (ROS) [21].

The first study showed strong antimicrobial behavior of both GO and rGO by deactivating the 98.5% and 90% of *Escherichia coli* (*E. coli*) DH5 $\alpha$  cells [22].

A study by He et al. evaluated the antibacterial activity of GO nanosheets against three common types of bacteria *Streptococcus mutans* - *Porphyromonas gingivalis* and *Fusobacterium nucleatum* against oral pathogens and found that GO nanosheets are very effective in inhibiting the growth of these pathogens. At a GO concentration of 40  $\mu\text{g} / \text{ml}$ , the growth of *P. gingivalis*

and *F. nucleatum* bacteria was inhibited, while at a concentration of 80 µg / ml, GO completely killed all *S. mutans* [23].

Subsequently, the broad-spectrum antimicrobial activity of GO was demonstrated by evaluating the antimicrobial activity against the phytopathogen and fungal species [24].

Antibacterial role of nano-graphene oxide was investigated by Wu et al. Thus they investigated whether the graphene oxide (GO) nanosheets could be used to enhance antibacterial activity of ASwalR RNA for *E. faecalis* in periapical periodontitis. They showed that GO-PEI could efficiently deliver the ASwalR plasmid into *E. faecalis* cell. GO-PEI-ASwalR significantly reduced virulent-associated gene expressions. Furthermore, GO-PEI-ASwalR suppressed biofilm aggregation and improved bactericidal effects [25].

GO also has the potential for drug delivery [26].

Properties such as biocompatibility and low toxicity of GO open up the scope of its application for the delivery of therapeutic drugs in the environment of these drugs BMP-2 aspirin [27], vancomycin

[28] and miRNA [29,30]. Many of the graphene-based drug/gene delivery systems such as nanocomposites of GO with vascular endothelial growth factor (VEGF) or GO carrier containing mitoxantrone have been developed as cardiac tissue regeneration systems or a therapeutic treatment for tumors [31].

The antibacterial properties of GO can be useful for dentists in various industries.

The antibacterial properties of GO can be very helpful in suture fabrication. It has been suggested that compared to conventional polyvinyl alcohol (PVA) fiber, which does not have antimicrobial properties. A PVA matrix dispersed with mechanically exfoliated graphene (MEG) exhibits a high antibacterial effect and thus effectively accelerates wound healing, making PVA/MEG nanocomposite fiber a promising new candidate for surgical sutures [32].

Further in-depth experimental studies are needed to further analyze the bactericidal effect of graphene for future clinical applications, especially with respect to dental pathogens, as these *in vivo* studies are still in their infancy. Applications of Graphene Oxide (GO) in Bone Tissue Engineering. Bone regeneration is a complex and dynamic physiological process that at the macroscopic level includes local mechanical stability, environmental matrix and blood supply, and microscopically includes the interaction of many cells, signaling molecules and effectors in a spatio-temporal sequence. The bone graft materials substitute should have the following characteristics:

- 1) good biocompatibility
- 2) suitable mechanical properties to ensure adequate durability;
- 3) porous structure or rough surface to facilitate the germination of cells and tissues;
- 4) favorable osteoconductivity and osteoinduction to stimulate the formation of new bone;
- 5) controlled degradability to match the rate of germination of new bone;
- 6) non-immunogenicity to ensure safe clinical use.

The extraordinary mechanical and electronic properties of graphene-based materials have motivated researchers to use them in tissue engineering and regenerative medicine [33].

Graphene and its derivatives provide a new selection for enhancing the mechanical and surface properties of biomaterials to regulate the cardiomyogenic, neurogenic, osteogenic and cartilaginous abilities of stem cells [34].

It is obvious that with these key multifunctional properties, graphene derivatives have shown their potential and became favorite materials for many biomedical scientists, to design new materials or hybrid materials or coatings of these nanomaterials to existing biomedical devices to overcome with the possibility of device associated infections.

Thanks to its unique characteristics, graphene quickly became a potential candidate for biomedical use. Overall, graphene-based materials hold great promise for application in different fields of medicine, more specifically in dentistry [35].

Its mechanical properties, including strength, stiffness, and flexibility, make it one of the most anticipated materials for bone engineering and may hold the promise of using Graphene in bone regeneration.

Good electrical conductivity of GO can not only directly stimulate the osteogenic activity of cells, but also indirectly adsorb active factors, promoting bone formation [36].

Thus, the properties of GO fully meet the requirements of dentistry and tissue engineering.

Lee et al investigated the ability of graphene oxide (rGO) and hydroxyapatite (HAp) (rGO / HAp NCs) to enhance osteogenesis of MC3T3-E1 preosteoblasts and new bone formation [37].

The following study conducted by Nizami et al assessed the efficacy of functionalized graphene oxide (f-GO) nanocomposites on the decalcification of dentin, because dental caries of the root surface is becoming one of the new problems in aged society [38]. GO-Ag and GO-Ag-CaF<sub>2</sub> almost completely inhibited *S. mutans* growth. However, they did not exhibit cytotoxicity to epithelial cells except at the highest concentration (0.1 w/v%) of GO-Ag and GO-Ag-CaF<sub>2</sub>. Furthermore, these f-GO nanocomposites exhibited less or no discoloration of dentin, although commonly used silver diamine fluoride causes discoloration of dentin to black. Thus, these f-GO nanocomposites are useful to protect dental caries on the tooth root that becomes a social problem in aged society [39].

The study of osteogenic mechanisms can indicate the right direction for further research; then, elucidating the mechanisms of degradation and metabolism will help to understand the space-time distribution of GD in vivo [40].

Ahn et al investigate the effects of mesoporous bioactive glass nanoparticle (MBN)/graphene oxide (GO) composites on the mineralization ability and differentiation potential of human dental pulp stem cells (hDPSCs) [41].

MBN/GO regulated the mRNA levels of odontogenic markers (dentin sialophosphoprotein (DSPP), dentine matrix protein 1 (DMP-1), ALP, matrix extracellular phosphoglycoprotein (MEPE), bone morphogenetic protein 2 (BMP-2), and runt-related transcription factor 2 (RUNX-2). MBN / GO composites promote differentiation of hDPSCs into odontoblast-like cells and potentially induce dentin formation [42]

### **Applications of Graphene Oxide (GO) in Periodontology**

Periodontitis is a destructive inflammatory disease, in which all periodontal tissues are generated, which leads to a decrease in the supporting system of the tooth. To increase the regenerative properties of bone materials, require tissue engineered scaffolds with optimized properties, including biocompatibility, osteoinduction, and controlled drug release.

However, with advanced periodontitis, the effectiveness of these strategies is insufficient, which dictates the development of new biomaterials to improve the quantity and quality of periodontal tissue regeneration. The use of nanotechnology can open up new horizons in the treatment of periodontal disease [43].

He et al. have found in their research that GO nanosheets are very effective in suppressing the growth of dental pathogens and will be an effective antibacterial material, and their use in periodontal therapy has promising potential [44].

Nanocarbon materials of the medium of which GO have begun to be used as a scaffold for collagen membranes, which will improve the regenerative therapy of periodontal disease in advanced periodontitis. To apply GO to tissue engineering therapy of periodontal disease, some researchers have created GO composite scaffolds. Research ensure good engraftment of cells, preservation of cell viability and proliferation, stimulation of spontaneous differentiation of osteoblasts and, importantly, stimulation of a higher physiological synthesis of cement [45-47].

During periodontal surgery, Radunovich et al. attempted to modify the collagen barrier membrane to improve its biocompatibility. The results showed that GO coating induces PGE2 secretion, controls inflammation, and promotes DPSC differentiation, which is likely [48].

Animal studies by Kawamoto showed that the GO scaffold promoted the formation of tissue like the periodontal ligament and cementum, followed by the formation of alveolar bone [49].

Research shows that the GO scaffold is biocompatible and has excellent bone and periodontal tissue formation properties, and therefore, the use of the GO scaffold in periodontal surgery can improve the effectiveness of periodontal tissue engineering therapy [50].

### **Potential Applications of Graphene Oxide (GO) in Endodontics**

Root canal treatment involves cleaning the infected root canal system; however, in some cases, endodontic failure is due to persistent infection in the root canal. In endodontics, there are still serious problems in removing the most bacterial infection from the root canals of the teeth. The unique antibacterial properties of nanomaterials hold promise in endodontics as they have superior properties when it comes to surface chemistry and bonding. Graphene based materials have potentials for dental and medical applications.

NiTi tools used in root canal treatment can improve their anti-corrosion quality due to the coating of their GO surface. Srimaneepong V. et al. in their studies have shown that GO-coated NiTi and GO / Ag-coated NiTi alloys have better corrosion resistance, lower corrosion rate and higher protection efficiency than uncoated NiTi alloy [51].

For the treatment of perforation, pulp coating and retrograde root filling in endodontics, bioactive cement is used, the addition of graphene nanosheets improves the mechanical properties of biocement and significantly reduces the setting time. In root canal treatment, biofilm is the cause of many failures, nanomaterials can provide better bactericidal properties of materials [52].

A study using GO in combination with silver nanoparticles showed strong antibacterial properties with less cytotoxic effect on soft tissues and bones compared to 3% sodium hypochlorite, which makes graphene a promising material for irrigation of infected canals in the future. In endodontics, graphene can also be added to bioactive cements Biodentine (BIO) и EndocemZr (ECZ), which shortens the setting time of the cement by reducing induction and accelerating the hydration process [53-55].

Adding GO to dental cements leads to a crushing of the porous structure, which not only strengthens the cement material, but also blocks the entrance for possible bacterial invasion. sealer mixed with fluorinated graphene has shown the best antibacterial effect over all time periods [56]. It should be noted that in the future it is worth continuing research on graphene due to its unique properties, which can expand its clinical application in endodontics, due to its biocompatibility and antibacterial properties.

### **Potential Applications of Graphene Oxide (GO) in Restorative Dentistry**

Secondary caries is considered a major cause of failure in dental restorations. Glass ionomer (GI) is widely used in restorative dentistry and graphene-based materials have great potential when used as fillers for polymeric dental adhesives due to their antibiotic film and bactericidal properties against pathogens such as *Streptococcus mutans*. A study by Bregnocchi A. et al. showed a significantly lower viability of *S. mutans* cells was demonstrated upon contact with Graphene-based dental adhesive [57]. Graphene combined with glass ionomer obtained with poly (acrylic acid), has significantly improved biomechanical properties of the gastrointestinal tract [58]. This combined material also decreases microcracks in the internal structure and protects it from erosion and disintegration by microbial invasion. A study by C. Sarosi, et al. showed an improvement in the degree of surface properties of resin polymer matrices when using graphene gold nanoparticles as fillers [59]. The antibiotic film and anti-adhesive properties of GO and its nanocomposites have inspired researchers to develop to prevent biofilm and caries formation.

### **Potential Applications of Graphene Oxide (GO) in prosthodontics**

The mechanical and biological properties of graphene oxide in combination with PMMA create superior flexibility, weight and biocompatibility compared to other materials previously used in dentistry. Due to its unique properties such as high bending strength, aesthetics, high appearance abrasion resistance, after adding graphene makes acrylic resin - an improved material [60]. Azevedo L. et al. in his research has shown that the addition of graphene oxide (GO) to polymethyl methacrylate (PMMA) resin for prosthetic rehabilitation increases the

mechanical properties of the prosthesis and decrease the degree of contraction during polymerization [61].

### **Potential Applications of Graphene Oxide (GO) in dental implantology**

The main reason for the loss of teeth is the complication of caries and periodontal disease, as a result of which patients have not only functional and aesthetic problems, but also worsen life quality. Currently, has become the traditional method of treating patients with tooth loss, however, dental implantation failures are still reported. The problem of restoring the lost tissues of the alveolar bone due to inflammatory processes and injuries is very urgent; for this purpose, such engineering and regenerative medicine have found wide application. Autogenous and various bone materials are widely used to augment bone tissue for dental implantation and to repair defects in the maxillofacial region resulting from removal of tumors.

Numerous factors leading to the of implants failures, an important role is played by the influence of anaerobic bacteria on the tissue around the implant. One of the solution to this problem is the modification of the surface of implants to optimize osseointegration. Biocompatibility is a fundamental requirement for both implants, currently, the company developers of dental implants use various methods of surface treatment of titanium dental implants; the use of new methods of nanotechnology can increase the osseointegration properties of dental implants.

To improve the interaction between implants and the bone tissue interface, the surface properties of implants, such as porosity, hydrophilicity, biomineralizability, cellular adsorption, can be improved by applying nanomaterials [62].

GO provides delivery of biomolecules and provides sites for cell adhesion that provides for bone regeneration. Recently, antibacterial materials have attracted attention in the field of dental implants; the use of graphene oxide nanocomposite on the surface of the implant to reduce the adhesion of bacteria is considered promising [63-65].

In some studies, graphene and GO have been used as coatings for dental implants. The GO coating confers increased proliferation, adhesion and osteogenic differentiation on the titanium SLA surface. In vivo, SLA/GO implants have been shown to exhibit excellent osseointegration characteristics [66,67].

Further in-depth experimental studies are needed to further analyze the antibacterial properties of GFN against dental pathogens.

Studies have shown that changes in the characteristics of titanium implants, such as surface composition, hydrophilicity, roughness topography and surface geometry, can affect the rate and quality of osseointegration [68].

To improve the surface of implants, Graphene and its derivatives, when applied to a titanium implant, have the ability to improve osseointegration, which puts them at the center of attention for modifying implant materials. GO can promote biomineralization and the formation of bone-like apatite on the implant surface, thereby improving osseointegration. Graphene and its derivatives, when applied to a titanium implant, have a remarkable ability to enhance the

properties of titanium, these characteristics put them at the center of attention for improving osseointegration and modifying implant materials. When GO is deposited on a titanium substrate, the hydrophobic nature of the graphene film has a self-cleaning effect on its surface, contributing to better osseointegration. The results confirmed that graphene coating of titanium may be a promising strategy for improving osseointegration and preventing biofilm formation on implants and devices.

Compared to titanium alone, graphene has osteogenic properties, increasing the expression of osteogenic genes and the protein osteocalcin and, therefore, increasing the deposition of mineralized matrix [69].

Jang et al. determined the effects of GO deposition (on a zirconia surface) on bacterial adhesion and osteoblast activation in order to reveal how direct-deposited graphene oxide on dental implants influences antimicrobial activities and osteogenesis. It was found that GO coated zirconium oxide inhibited *S. mutans* attachment and stimulated osteoblast proliferation and differentiation, which could prevent peri-implantitis by inhibiting bacterial adhesion. Moreover, its osteogenic ability can increase bone adhesion and success rate of implants [70].

Nanotechnology can be considered a disruptive technology as it can have many different uses and replace older technologies [71].

In this review we presented summary of the latest research progress related to the potential applications of Graphene oxide in dentistry.

A literature review showed that GO improved the physical, chemical, and mechanical properties of biomaterials, in dental field. GO is not only making its way into dentistry; it could be a revolutionary technology in dentistry.

Although in the presented studies the use of materials based on e GO in various areas of dentistry has shown promising results, many problems remain to be solved before their clinical use.

The follow-up period in existing studies is insufficient, therefore studies longer than 1 year should be encouraged. Most of the studies have been applied to animal models (rats and rabbits); moreover, the mechanism of interaction between GO and the in vivo environment after implantation requires further clarification.

Consideration should be given to cost-effectiveness, cost and availability as the technology for manufacturing and processing GO is limited due to the complexity of large-scale synthesis. Cost can also be a barrier to further research.

Thus, despite various challenges, GO is likely to represent a real breakthrough for future research in dentistry, and advances in related technologies will pave the way for earlier clinical use of GO. We hope this review article can provide valuable insight into future scientific and technological innovations of graphene in dentistry.

## CONCLUSION

From this review, it can be concluded about the prospects for future developments, the use of Graphene in dentistry. Graphene oxide (GO) has the potential for future clinical applications in a variety of dental applications.

## Declaration of Competing Interest

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