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Review article

Impact of graphene incorporation in dental implants–A scoping review

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ABSTRACT

There are numerous variables governing the formation of new bone around a dental implant. Of those variables, the implant surface is an important factor influencing the quality of osseointergration. Numerous techniques and materials have been used to alter the surface of an implant to enhance osseointergration and improve the survival and success rate. One such modification is utilizing graphene to modify the surface of an implant. This paper summarizes data collected form articles published in online databases in the past 10 years about the various means of modifying the implant surfaces and provides an in-depth review of the impact of graphene incorporation in dental implants.

The document comprised of different sections and emphasized on the use of graphene as an implant surface coating material. The role of graphene on flexural strength, hardness and corrosion resistance have been discussed under mechanical properties whereas the potential of this combination on the osteogenesis, osseointergration and soft tissue seal is covered under biological properties. Lastly, how this combination acts as a drug delivery carrier and renders antimicrobial property has been addressed under pharmacological properties.

This review has highlighted the various applications of graphene in the field of implant dentistry. It has outlined the various implant surface modifying methods and thrown light on the various affect this combination has on the mechanical, biological and pharmacological properties. Considering the various research done on the material, it can be concluded that graphene does have a bright future in implant dentistry and continued research in this area will provide fruitful benefits.

Statements and declarations

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1. Introduction

Prosthetic rehabilitation using dental implants has seen a paradigm shift in the last 10 years. As people are becoming aware about implant restorations, this form of treatment is gaining popularity. Implants are basically made of three components namely the fixture or the body of implant, the abutment, and the crown [1]. The abutment and the crown can either be available as two separate units, or they can be fabricated as a single unit and then attached to the implant (Fig. 1).

Branemark, many years ago coined a term osseointegration and defined it as *"The direct connection, structural and functional, between new bone and the surface of implant"*. There are many factors which are responsible for successful osseointegration. One of the numerous variables which govern how new bone forms around an implant, are the features of the implant surface. The research by Osborn and Newesley [2] has shown that distant osteogenesis and contact osteogenesis are the two processes by which new bone is formed around a dental implant. In distant osteogenesis, bone deposition and mineralization happens from the periphery towards the implant whereas in the second phase, it occurs in the opposite direction, i.e., from the implant towards the periphery. The quality of osseointegration is directly related to the type of implant surface [3]. Lately, there has been a greater focus on the different implant surface topography instead of the earlier, which focused on implant shape for improved osseointegration.

Amongst all the different materials on offer, a plentiful element with significant uses in science and technology is carbon. There are four main categories of carbon nanostructures (zero, one, two and three-dimensional) which are based on the spatial arrangement of the carbon atoms. Of these, the two-dimensional planar arrangement of carbon atoms forms a chemical compound called graphene [4] which has remarkable mechanical, electrical and thermal properties. The study of synthetic nanomaterials based on graphene that can be used as nanomedicines in dentistry is an expanding area of study. Graphene may also be functionalized with a variety of bioactive compounds, enabling them to be used in regenerative dentistry [5].

Xiaojing Li[6]and his colleagues in their work have put forward an extensive summary of the various field within dentistry where graphene can be incorporated. These include tissue engineering, antibacterial application, collagen membrane, adhesive cements and silane primers, detection of bacteria, PMMA resin additives, teeth whitening and dental implant coatings.

Another interesting area of graphene application is as a host immune modulator. It has been seen in the work of Srimaneepong et al. [7], that graphene-based materials may cause a change in the levels of cytokine released in the body. They tested the cell viability of human pulp fibroblast, IL-6 & IL-8 levels against NiTi coated alloys and found that both, GO-coated NiTi and GO/Ag-coated NiTi alloys showed better corrosion resistance and higher protection efficiency than the bare NiTi alloy. The coated samples also showed an upregulation of all the host immune cells namely IL-6 and IL-8.

Speaking of implant dentistry, there has been a lot of work happening with graphene as a potential surface modifying agent. As stated above, implant surface modifications are mainly done to enhance osseointegration. Zhu et al. [8], in their review threw light on the different methods available for altering the surface of a dental implant. For ease of understanding they classified the methods into different groups namely mechanical, physical, chemical, and biologic and have spoken about each of them in brief. However, the influence of graphene and its derivatives on dental implants seems lacking.

This paper intends to highlight the various modalities of incorporating Graphene on dental implant surfaces and the effect of this combination on mechanical and biological properties of implants. The various effects have been discussed under mechanical, biological, and pharmacological properties. The positive effect of the combination on the flexural strength, corrosion resistance, and tribological properties has been discussed in detail under mechanical properties. The effect of graphene on enhancing soft tissue seal around implants and the impact on resulting osseointegration have been listed under biological properties. Lastly, the ability of this combination to inhibit the microbial growth has been described under the pharmacological section. Though this review, the reader will get a complete idea of how the current situation holds in terms of graphene and dental implants and will get a fair idea of what the future could hold in this regard.

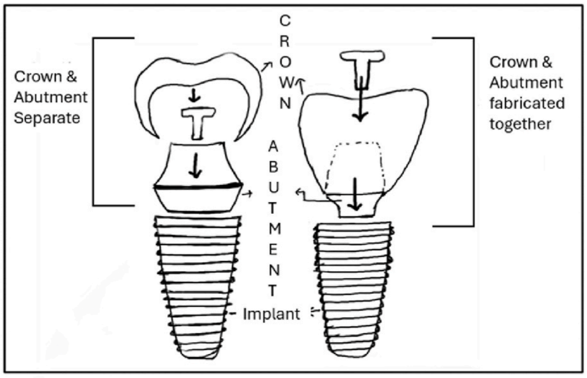

Fig. 1. Components of dental implants.

2. Material and methods

An electronic search was performed within the online databases (PubMed, Scopus, Cochrane & Embase) using the search string "Graphene AND (Dental Implants). Only full-length articles written in English language from the past 10 years were selected for the review. Any form of review articles and studies which used graphene in conjunction with other material were not selected.

The search from all the databases resulted in a total of 203 articles. After removing duplicates, a total of 125 articles were shortlisted. Following manual filtration, a total of 74 articles (reviews and original study) were selected. Of the 74 articles, removal of reviews left us with a total of 60 articles (Fig. 2).

3. Methods of implant surface modification

The contact between the implant and the bone can be influenced by the surface of the implant [9]. Rougher surfaces can promote adhesion, differentiation, and proliferation of bone cells, which leads to the development and mineralization of bones. Therefore, most efforts are directed in trying to make the surface rough. The wettability and surface energy that are essential for blood implant interaction are accounted for by the hydrophilicity of the implant surface. Electrochemical functionalization can improve this. Likewise, a lot of different materials and methods have been employed with the idea of enhancing the overall treatment progress of implant restorations. A detailed classification of the different methods to alter the surface characteristics as given by Zhu et al. [8], is summarized in Fig. 3.

3.1. Mechanical modification methods

These methods are generally employed to smoothen or roughen the surface, remove surface contamination and to prepare the surface of the biomaterial for further treatment. They alter the surface characteristics (biological adhesion, surface hydrophilicity, bone tissue affinity, electrical potential energy, surface tension) of the dental implant which influence the process of osseointegration.

Eg- Grinding, Polishing, Sand blasting, Vacuum Annealing.

3.2. Physical modification methods

The dry conversion of passive, inert implants into intelligent implant surfaces that actively direct the physiological environment towards bone tissue regeneration often involves physical change. Typically, little or very little chemical reaction occurs during the entire process of surface modification when using physical modification methods.

Eg – Plasma Spraying, Plasma immersion ion implantation, laser cladding.

3.3. Chemical modification methods

The substrate-medium interface is typically the site of a violent chemical reaction in chemical modification techniques. The reaction frequently involves heating, redox reaction, luminescence, and other phenomena.

Eg - sandblasting and acid etching, thermal oxidation, hydrothermal treatment, anodic oxidation, and micro arc oxidation.

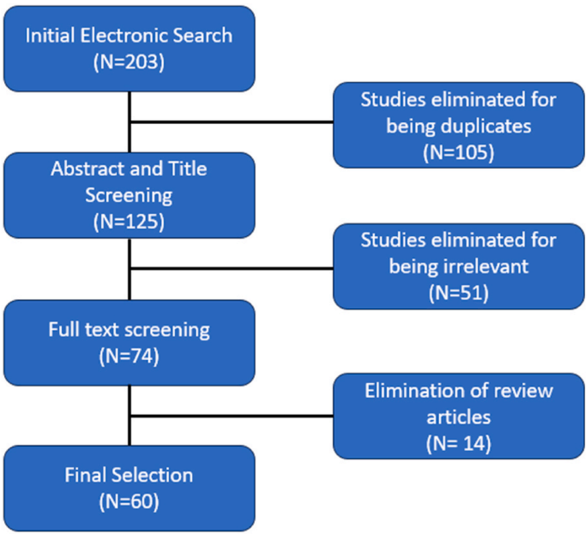

Fig. 2. Search strategy.

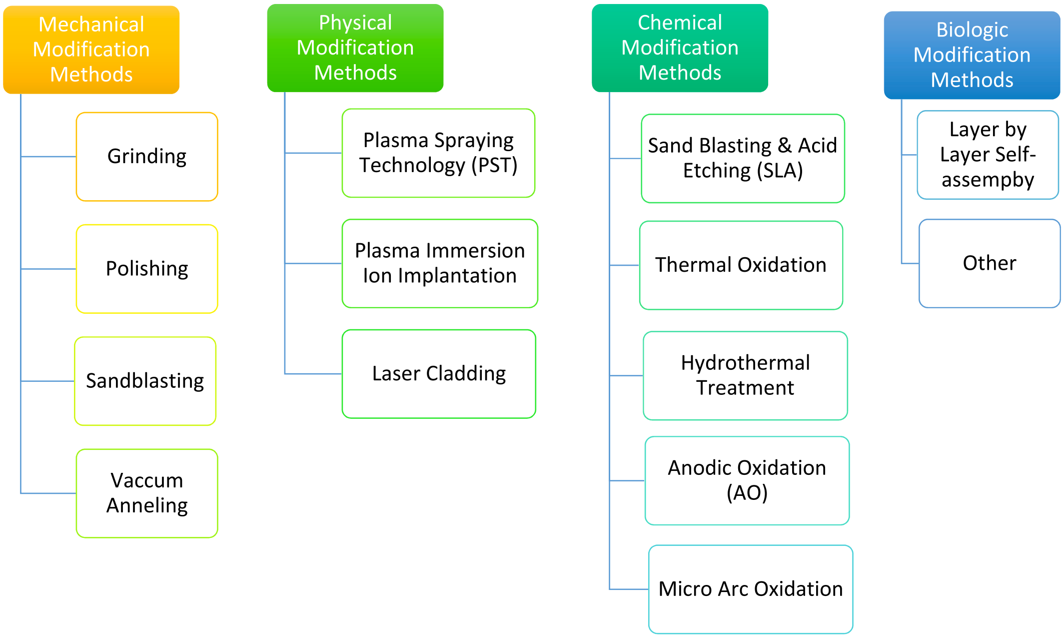

Fig. 3. Various Surface modifying methods.

3.4. *Biologic modification methods*

Specific bioactive materials, like proteins, peptides, and enzymes, are fixed to the implant surface through biological modification techniques. The biologically modified implant surface stimulates the adsorption of various proteins from the internal environment after implantation in the body, resulting in the formation of a protein layer. This induces events such as cell adhesion, migration, proliferation, differentiation, and apoptosis that can aid in tissue formation, osseointegration, and other biological processes. These bioactive layers can offer active sites for a variety of biological responses involving cellular receptors. Biological surface modification is more direct and effective than physical and chemical modification techniques.

4. Graphene

The main critical element in Graphene is carbon. The atomic configuration of graphene as explained by Tahriri et al. [10], shows how graphene offers significant mechanical properties. They also speak of the main derivate of graphene namely graphene oxide and

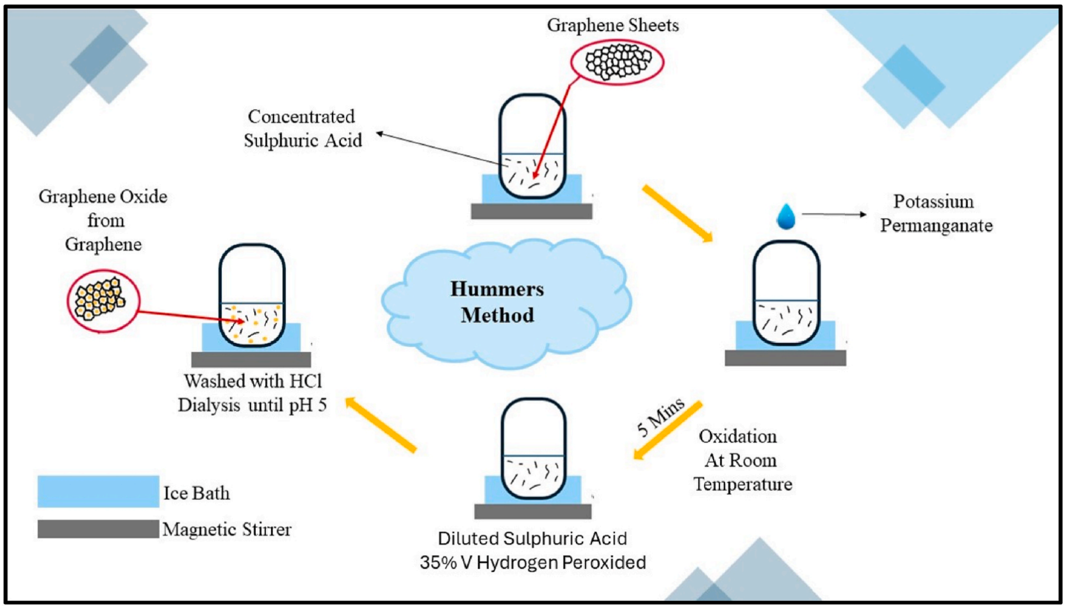

Fig. 4. Schematic representation of the Hummers' method.

reduced graphene oxide. The oxidation of graphite leads to the formation of graphene oxide whereas, if graphene oxide is reduced, it will lead to the formation of reduced graphene oxide. Though both these materials have significant applications, graphene oxide allows the attachment of a variety of functional groups which make them suitable for wide range of purposes especially biomolecules for wide range of bio-applications.

4.1. Synthesis of graphene

The three main ways to make graphene are chemical vapor deposition, exfoliation, and chemical-based methods[11–13]. To acquire the necessary qualities of graphene sheets, the sheets must be separated from one another; otherwise, they are prone to combine and create crude graphite structures, which is one of graphene's critical characteristics.

Mechanical exfoliation – Multiple sheets of graphene which are held together by van der Waals interaction form graphite. Thus, to harness graphene from graphite, these van der waals bonds need to be cleaved so that sheets of graphene can be individually separated. This was performed with the Scotch-tape method.

Chemical vapor deposition (CVD) – this is the best method of producing graphene. The process involves catalytic decomposition of hydrocarbons on the surface of a metal catalyst. Advantage of this method include the absence of or low amount of metallic residuals and the possibility to synthesize heteroatom-doped graphene nanostructure. This allows for addition of compounds such as nitrogen,

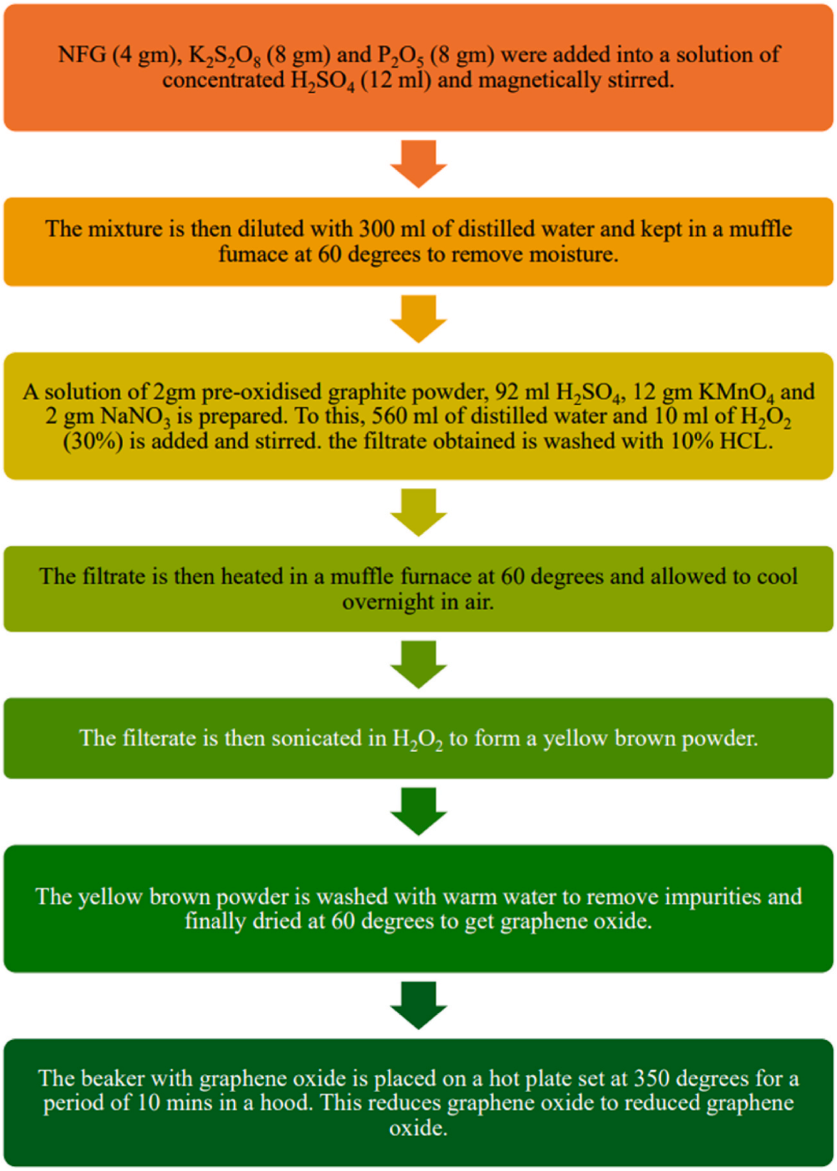

Fig. 5. Schematic representation of modified hummers method.

sulphur, phosphorous and a few halogens to graphene which enhances its performance.

Chemical based methods – the above-mentioned methods are preferred for precise devise assembly; however, they are not very effective for large scale production of graphene. One of the most effective processes for producing graphene and its derivatives on a large scale is chemical-based synthesis[13–15]. Large amounts of graphene can be produced chemically, however some of these methods call for unique or expensive ingredients. In the year 1859, the first procedure to develop graphene oxide was put forward by Brodie [16]. In his work, he demonstrated how graphene can be obtained from graphite slurry using potassium chlorate in the presence of fuming nitric acid. Staudenmaier improved on this method in 1898 by combining fuming nitric acid and strong sulfuric acid, then gradually adding chlorate to the reaction mixture. This minor modification to the process resulted in a straightforward and updated approach for the manufacture of highly oxidised GO. The Hummers' method (1958), which uses graphite as a carbon precursor and concentrated sulfuric acid as an oxidant in the presence of KMnO4, is the most well-known method [17]. Water and oxygen peroxide are introduced to separate the graphene oxide sheets after keeping the reaction at the optimum temperature. The sheets are then cleaned with water and hydrochloric acid (Fig. 4).

The workflow for the modified hummers method of producing graphene oxide is shown in Fig. 5. They successfully prepared graphene oxide by oxidising purified natural flake graphite which was later thermally reduced to synthesize reduced graphene oxide. While rGO and natural flake graphite were discovered to be hydrophobic in nature, GO's hydrophilicity allows it to dissolve easily in solvents like water. According to the results of the thermal investigation, rGO is more thermally stable than GO. Electrochemical modification of graphene is a different chemically based procedure for producing graphene. By providing a constant voltage to a graphite anode and cathode in an electrolytic solution of deionized water and ionic liquids, such as imidazolium, this technique produces graphene sheets [18].

All the above-mentioned methods highlight how graphene and its derivatives, namely graphene oxide and reduced graphene oxide are produced from graphite. Once produced, these materials can be used in different fields of dentistry. One such area of interest is in the use of graphene and its derivatives in implantology. Graphene and its derivatives have seen a wide range of applications with dental implants to counter several shortcomings. To understand better, the various properties which are seen to gain a boon can be classified into two broad groups namely mechanical and biological. The following text aims to throw light on these properties and understand better how graphene and its derivate influence dental implants.

4.2. *Surface treatment of dental implants with graphene*

This sections elaborates on how graphene is coated on to the implant surface. A titanium dental implant needs an effective surface treatment for tissue regeneration and for this purpose, various treatment methods have been used. Park et al. [19], in their work have highlighted different methods for the same as given by different authors. The various methods along with their authors is given in Table 1 below.

5. Effect of graphene on dental implants

Graphene and its derivatives have seen a wide range of applications with dental implants to counter several shortcomings. To understand better, the various properties which are seen to gain a boon can be classified into three broad groups namely mechanical, biological and pharmacological and are summarized in (Table 2). A brief description about each property is given in the section below.

5.1. *Mechanical properties*

Materials in the form of restorations or prosthesis when placed intraorally, are subjected to a wide range of loads from all directions [20]. Occlusal forces make up for the bulk, but lateral forces are not negligible as well. Thus, materials need to possess character to withstand these forces and not fracture under them. Properties such as flexural strength, hardness & corrosion resistance need to be assessed to evaluate the behavior of a material over a longer duration of time.

5.1.1. *Flexural properties*

In the field of health science, flexural properties give a measure of the amount of force that a material can withstand without undergoing plastic deformation. When an implant is placed intraorally, it is exposed to multidirectional forces which it must withstand. The ability of the implant to withstand these forces is rendered by the material from which it is fabricated. Thus, the elastic behavior of each material is thoroughly tested before it is tried on clinically. Conventionally, dental implants are manufactured from

Table 1
Surface treatment methods of dental implants.

Year	Author	Name of Method
2007	Rojas and Leiva	Modified graphene sheet decorated with titanium
2013	La et al.	Layer-by-layer assembly (LbL assembly)
2015	Kalisz et al.	Poly(methyl methacrylate) (PMMA) mediated method
2004	Fukada et al.	Electrophoretic deposition
2016	Jung et al.	Spin coating

Table 2
Effect of graphene incorporation on various properties.

Author	Title	Intervention	Property tested	Results	Conclusion
Mechanical Properties					
V Patil et al.	Biomechanical Behavior of Bioactive Material in Dental Implant: A Three-Dimensional Finite Element Analysis	The titanium was functionalized with graphene and graphene oxide. A modeling software tool Catia and Ansys Workbench is used to perform the analysis and evaluate the von Mises stress distribution, strain, and deformation at the implant and implant-cortical bone interface.	Flexural Properties	The results showed that the titanium implant with a surface coating of graphene oxide exhibited better mechanical behavior than graphene, with mean von Mises stress of 39.64 MPa in pitch 1, 23.65 MPa in pitch 2, and 37.23 MPa in pitch 3	functionalizing the titanium implant will help in reducing the stress at the implant system.
M Kalisz et al.	Comparison of mechanical and corrosion properties of graphene monolayer on Ti–Al–V and nanometric Nb2O5 layer on Ti–Al–V alloy for dental implants applications	comparative studies on structural, mechanical and corrosion properties of Nb2O5/Ti–Al–V and graphene/Ti–Al–V alloy systems have been investigated	Surface Hardness	Hardness of pure niobium pentoxide was 8.64 GPa and graphene deposited on titanium alloy surface was equal 5.63 GPa.	The graphene monolayer has no effect on surface hardness of titanium alloy however, ot did improve the corrosion resistance.
			Corrosion Resistance	the sample with graphene coating has much better corrosion resistance.	
AML Rocha et al.	Functionalization of titanium dental prostheses surface with antimicrobials GO and Cu2O	functionalization of titanium abutment surface with antimicrobials graphene oxide and copper oxide. The samples were divided into 4 groups: G1 (Cu2O coating); G2 (GO coating); G3 (GO + Cu2O coating) and G4 (no coating).	Surface roughness	After surface functionalization, all groups had adequate roughness values for soft tissue sealing, less than 0,4 μm.	
			Wettability	G1 samples had the lowest wettability (2.16 ± 6.23 mJ/m2). G4 samples had the highest wettability (38.57 ± 10.51 mJ/m2)	
Biological Properties					
Qingfan Li and Zuolin Wang	Involvement of FAK/P38 Signaling Pathways in Mediating the Enhanced Osteogenesis Induced by Nano-Graphene Oxide Modification on Titanium Implant Surface	nano-GO was deposited on the SLA surface via an ultrasonic atomization spraying technique to create the SLA/GO group	Osteogenesis	The GO-modified surface favored cell adhesion and spreading, and significantly improved cell proliferation and osteogenic differentiation of BMSCs	GO modification on titanium implant surface has potential applications for achieving rapid bone-implant integration through the mediation of FAK/P38 signaling pathways
MS Kang et al.	Reduced graphene oxide coating enhances osteogenic differentiation of human mesenchymal stem cells on Ti surfaces.	Human mesenchymal stem cells (hMSCs) were cultured on the rGO-Ti substrate, and then their cellular behaviors such as growth and osteogenic differentiation were determined by a cell counting kit-8 assay, alkaline phosphatase (ALP) activity assay, and alizarin red S staining.	Osteogenesis	While rGO-Ti substrates significantly increased cell proliferation after 7 days of incubation, they significantly promoted ALP activity and matrix mineralization, which are early and late differentiation markers, respectively	It is suggested that rGO-Ti substrates can be effectively utilized as dental and orthopedic bone substitutes since these graphene derivatives have potent effects on stimulating the osteogenic differentiation of hMSCs and showed superior bioactivity and osteogenic potential
Shin et al.	Enhanced osseointegration of dental implants with reduced graphene oxide coating	SLA Ti (ST) implants with different surface modifications [i.e., rGO and recombinant human bone morphogenetic protein-2 (rhBMP-2)] were prepared and investigated for their dental tissue regenerating ability in animal models.	Osseointegration	In vitro and in vivo studies revealed that the R-ST group showed significantly better effects in cell attachment and proliferation, alkaline phosphatase activity, matrix mineralization, expression of osteogenesis-related genes and protein, and osseointegration than the control (ST), BI-ST, and BT-ST groups.	The rGO-coated Ti can be a promising candidate for the application to dental or even orthopedic implants due to its ability to accelerate the healing rate with the high potential of osseointegration.
J Wei et al.	Graphene-Reinforced Titanium Enhances Soft Tissue Seal	Fabricating a novel graphene-reinforced titanium (ti-0.125G) using the spark plasma sintering technique.	Mucointergration	The findings showed that the graphene-reinforced samples were very good at maintaining a balance between the positive fibroblast responses and the suppressive microbial development	Ti-0.125G has promising potentials for application in implant dentistry, especially in enhancing the integrity of soft tissue and improving its resistance against bacterial infections around oral implants
Pharmacological Property					
AML Rocha et al.	Functionalization of titanium dental prostheses surface with antimicrobials GO and Cu2O	functionalization of titanium abutment surface with antimicrobials graphene oxide and copper oxide. The samples were divided into 4 groups: G1 (Cu2O coating); G2 (GO	Antimicrobial action	The surface of G2 samples had the largest number of dead bacteria (226.334 AU/42.38 %). G4 samples allowed the greatest	

(*continued on next page*)

Table 2 (*continued*)

Author	Title	Intervention	Property tested	Results	Conclusion
		coating); G3 (GO + Cu2O coating) and G4 (no coating).		adherence of S. mutans strains (399.056 AU/ 32.10 %).	
W. G. La et al.	Delivery of a therapeutic protein for bone regeneration from a substrate coated with graphene oxide	Titanium (Ti) substrates are coated with GO through layer-by-layer assembly of positively ($GO-NH_3^+$) and negatively ($GO-COO^-$) charged GO sheets. Subsequently, a therapeutic protein (bone morphogenetic protein-2, BMP-2) is loaded on the GO-coated Ti substrate with the outermost coating layer of $GO-COO^-$ (Ti/GO^-).	Drug release	The extent of in vitro osteogenic differentiation of human bone marrow-derived mesenchymal stem cells is higher when they are cultured on Ti/GO- carrying BMP-2 than when they are cultured on Ti with BMP-2. Eight weeks after implantation in mouse models of calvarial defects, the Ti/ GO-/BMP-2 implants show more robust new bone formation compared with Ti, Ti/GO-, or Ti/BMP-2 implants.	GO is an effective carrier for the controlled delivery of therapeutic proteins, such as BMP-2, which promotes osteointegration of orthopedic or dental Ti implants.

titanium and its alloys. However, the introduction of graphene in dental healthcare has opened doors for new combinations with titanium for their use in dental implants. Patil V et al. in the year 2020, tested the biomechanical behaviour of bioactive materials in dental implants. They studied the impact of thread design of the implant and three different bioactive materials i.e., titanium alloy, graphene, and reduced graphene oxide (rGO) on stress, strain, and deformation in the implant system using finite element analysis (FEA) as it provides valid and accurate assessment in the clinical and in vitro analysis. With mean von Mises stress of 39.64 MPa in pitch 1, 23.65 MPa in pitch 2, and 37.23 MPa in pitch 3, the titanium implant with a graphene oxide surface coating demonstrated superior mechanical behaviour compared to graphene, according to the data. According to the findings, graphene oxide coated titanium implants outperformed graphene titanium implants in terms of mechanical behaviour. It also showed that functionalizing the titanium implant will help relieve stress on the implant system which in turn reduced the chances of implant fracture [21].

5.1.2. Corrosion resistance

Dental Materials or dental restorative components placed intra-orally are in constant contact with saliva and other body fluids. Thus, in conjunction with air, makes it the most favorable situation for corrosion to take place. Materials such as chromium and titanium are well known for their inherent anticorrosive properties. These materials have the ability to form an oxide layer, chromium oxide and titanium oxide respectively, over their surface when they are exposed to the atmosphere which protects the inner metal from corrosion [22]. Titanium and its alloys which are commonly employed in the implant industry, have exhibited excellent mechanical properties and corrosion resistance when placed intraorally. However, with technological advancement and the advent of new products for maintenance of dental hygiene, fluoride containing oral hygiene aids are gaining popularity. Halogen, which has numerous positive effects on the dental hard tissue, is inimical to reactive mentals such as titanium. Fluoride reduces the passivity of titanium by disrupting the oxide layer, in turn increasing the chances of corrosion and reduces the wear resistance [23]. To overcome this, the implant surface is coated with niobium oxide (Nb2O5) or ultrathin graphene monolayer. Studies have shown that a single graphene layer considerably increases the corrosion resistance of such systems as copper/graphene and nickel/graphene and protects the surfaces of those metals from oxidation. Graphene Ag coatings can also help prevent corrosion [7].

In numerous studies the corrosion properties of titanium implants coated with graphene and niobium oxide was evaluated [24–28]. The results of these studies suggested that though graphene proved to be a better anticorrosion agent, it did not contribute significantly to the surface hardness and could be easily pulled off from the surface. Thus, the use of hybrid multilayer was proposed (combined layers of niobium pentoxide and graphene) which can greatly improve the mechanical and corrosion properties of the titanium alloy surface.

5.1.3. Surface hardness

the surface of dental implants coated with graphene do not show any change in the hardness values.

5.1.4. Tribological properties

Tribology is the study of the science and engineering of interacting surfaces in relative motion and includes the study and application of the principles of friction, lubrication and wear. The word tribology was derived from the Greek word “tribos” which literally means rubbing. Thus, this entity encompasses all the aspects that come into consideration between two bodies which are in a state of relative motion.

Following osteotomy for the desired implant dimension, as the implant is screwed into the bone, there is friction generated at the bone-implant interface. This resistance to an implant placement is dependent on the quality of the bone with D1 bone offering the maximum resistance. The use of a “screw-tap” in such scenarios creates channels in the bone which make implant placement easier. However, in such scenarios, having a material lining the implant & acting as a lubricant could influence the tribological properties. But a material placed between two hard structures in relative motion should possess good wear resistance. M. Kalisz et al., in their work in 2015, showed that the graphene monolayer deposited on the titanium alloy surface was not resistant to abrasion and is very easy to scratch and remove it from the alloy. Thus, graphene when coated on the implant will not fulfil the requirement for using it as it has a high chance to tearing off while it is being placed into the bone.

Apart from the bone-implant interface, the implant-screw interface is also one such junction where two hard surfaces come together. Wu et al. (2017) in their work incorporated a mixture of graphene and petroleum jelly at the abutment implant-screw interface to assess if there was any positive effect of the combination. However, this was not the case as lubricated screws resulted in lower de-torque values which made the joint easier to loosen. Thus, combination was of using a lubricant proved completely wrong. It may be advised for clinical use and future design to keep the implant screw inter-face free of any foreign material.

5.2. Biological properties

These properties encompass the various interactions between the dental implant and the biological system. Once the implant is placed in the osteotomy site, it first contacts blood. As the implant is screwed in further, it engages the bone surface apically which provides the primary stability. Over time, as the process of bone healing takes place, the bone lining the dental implant undergoes necrosis, a process termed as the “dieback phase”. This happens in the initial 18 days post implant placement following which, there is new bone formation i.e., osteogenesis.

5.2.1. Osteogenesis

As mentioned earlier in the text, new bone formation takes place by two processes i.e., distant and contact osteogenesis. The osteoblast present in the blood are stimulated to undergo differentiation and lay down the new bone matrix which mineralizes over time to form hard bone. Titanium, the most widely used material for implant fabrication has limited osteoinductive properties especially in compromised condition (poor bone quality & quantity) [29–32]. To overcome this, the implant surfaces are modified with different methods however, it still takes 3–6 months to achieve proper osseointergration. Therefore, more research was carried out in this direction to ultimately arrive at newer alternatives such a hydroxyapatite, graphene, magnesium, zinc, strontium and calcium to be applied over the already existing technology. Of these materials, graphene oxide has shown good application prospects in the biomedical field. Invitro studies by Kim et al. in the year 2009–2014 on graphene oxide and calcium carbonate composites showed positive results in terms of biocompatibility with osteoblasts and increased osteogenic property. Apart from these, several other advantages such as accelerating the differentiation of human mesenchymal stem cells (hMSCs), widespread use as a drug delivery agent and inherent antimicrobial properties showed that graphene has great potential as a surface modification agent [33].

In the year 2020, Qingfan Li and Zuolin Wang [33] studied on the rats the involvement of Nanographene oxide on the FAK/P38 signaling pathways in mediating the enhanced osteogenesis on titanium implant surface. This was primarily done to overcome the limited osteoconductive capability of titanium. As a part of their study, titanium dental implants underwent SLA treatment (sand blasting and acid etching) following which two groups were made. The specimens in the test group were coated with nano-graphene oxide via an ultrasonic atomization spraying technique whereas the control group did not receive any intervention. With increased hydrophilicity and protein adsorption, in-vitro analysis of GO-modified surface showed that the FAK/P38 pathway were involved in the osteogenic differentiation of bone marrow cells of rats. Also, there was an evident increase in cellular proliferation and osteogenic differentiation on the GO-modified implants.

In the following year i.e., 2021, Moon Sun Kang and his colleagues published their work wherein they investigated the effect of reduced graphene oxide (rGO) on osteogenic differentiation on human mesenchymal stem cells. Here, the rGO was uniformly coated onto the implant surface via the meniscus-dragging deposition (MDD) technique following which they were subjected to an array of physio-mechanical tests. The human mesenchymal stem cells (hMSCs) were cultured on the rGO-Ti substrate to assess the cellular behaviour. All the test performances were evaluated to finally conclude that rGO-Ti surfaces also significantly increased cell proliferation and matrix mineralization [34]. The results of this study were in accordance with the results of another study performed in the year 2017 by Xiaojing Li and his coworkers who also worked with rGO to see their effect on MC3T3-E1 cells (human mesenchymal stem cells). Their study results suggested that rGO coated titanium surfaces had osteoinductive potential and thus had a scope to be used for enhancing osseointergration.

5.2.2. Osseointergration

One of the crucial factors which enhance the long-term clinical success of dental implants is osseointegration. It is defined as, *"the intimate contact between living bone and implant surface without the intervention of fibrous connective tissue."* Amongst the various factors which determine the efficacy of osseointegration, implant surface characteristics hold the key in the initial stages of bone-implant contact [35]. This initial interaction has a significant influence on the later stages of osseointegration. Titanium, being an inert material, does not bond directly to bone and nor do they induce new bone formation [36]. Thus, a lot of research has been done in the past and is being done currently to enhance osseointergration. Sandblasting and acid etching has now become the basic minimal requirement of a dental implant surface treatment[37–39]. In order to improve osseointergration, Arg-Gly-Asp peptide, collagen and growth factors such bone morphogenic protein are increasingly being used as biomimetic molecular alterations on the surface of dental implants [40].

Graphene too, has shown positive results in terms of osteogenic differentiation and proliferation. In a study done by Shin et al. [41], the osseointegration of dental implants coated with reduced graphene oxide and recombinant human bone morphogenic protein −2 (rhBMP-2) was tested against the conventional SLA treated implants. Through different tests such as spectrophotometry diffractometry and microscopic analysis, it was confirmed that the surface modifying agents were coated well around the surface of test sample. Though the test results were in favor of the rhBMP-2 as a coating material, the performance of graphene was not far behind. Thus, it was suggested that rGo-coated titanium implants can be a promising candidate for accelerating the rate of bone healing with higher potential for osseointergration. Another study and another positive result for graphene. Rosa et al. [42], were determined to observe how the dental implant coated with graphene nanoparticles behaved under stressful conditions and to no surprise, it did enhance bone formation in vivo. Mechanical stress was not the parameter which was of concern. It was basically to assess the performance under biologically relevant stresses. Even in the presence of lipopolysaccharides, graphene nanoparticles, due to their high level of inertness, do not cause macrophages to express any inflammatory markers. Additionally, it resisted corrosion caused by microbes and maintained very good coverage and quality even after being exposed to biofilms for an extended period of time. These findings demonstrate that graphene is resilient to abrasive and inflammatory biologic conditions and that it preserves a promising level of structural integrity around dental implants' collars, a location that is particularly vulnerable to biofilms at the beginning of implant disease.

5.2.3. Soft tissue seal

Post implant placement, as weeks pass by, there are numerous changes taking place within the intraoral hard and soft tissue. After all, implant placement is an invasive procedure wherein we induce trauma following which the body is allowed to heal. To make this process of healing faster, there are several studies done with most being focused on the bone. In general, whenever the topic of dental implant comes up, osseointergration and bone implant contact are the only factors taken into consideration. The soft tissue which covers the bone is not given the due importance it deserves. It is the health of the soft tissue around the dental implant which governs its long-term success. If the soft tissue is healthy and forms a tight seal around the implant collar and the abutment, there will not be any food accumulation and plaque formation. This would prevent pocket formation which will eventually lead to bone loss and infection in the peri implant tissue. There are new techniques being employed in the field of implantology to enhance soft tissue health.

Photo biomodulation is one such therapy which basically encompasses the use of laser light for bringing about cellular responses [43].

Apart from lasers, graphene also has stomped its authority in terms of biocompatibility and antisepsis. Graphene is commonly used as a coating material. However, due to poor tribological properties graphene is seen to peel off from the implant surface. Thus, to counter this, Wei et al. [44], in the year 2021 fabricated a novel graphene-reinforced titanium (ti-0.125G) using the spark plasma sintering technique. This techniques ensured that the graphene was evenly spread out throughout the titanium and was bonded strongly. The test parameters were selected in such a way that it mimicked the oral environment to get better knowledge. To test the antimicrobial activity, instead of choosing one or two bacteria, a multi species biofilm containing typical pathogens of peri-implantitis like *Streptococci mutans (S. mutans), Fusobacterium nucleatum (F. nucleatum), and Porphyromonas gingivalis (P. gingivalis)* was constructed. In addition, a co-culture model involving the aforementioned pathogens and human gingival fibroblast was established to evaluate the soft tissue seal. In addition to having a strong inhibitory effect on *Porphyromonas gingivalis*, Ti-0.125G was generally efficient against a variety of pathogens as opposed to only one strain. The findings showed that the graphene-reinforced samples were very good at maintaining a balance between the positive fibroblast responses and the suppressive microbial development, which could be the reason for the best soft tissue seal in the oral cavity. Consequently, it is inferred that Ti-0.125G has promising potentials for application in implant dentistry, especially in enhancing the integrity of soft tissue and improving its resistance against bacterial infections around oral implants. However, there is not much said about the physical properties of this new novel material.

5.3. Pharmacological

Apart from the above-mentioned mechanical and biological uses of graphene in implant dentistry, it also encompasses a few pharmacological actions as well. This versatility of graphene is what makes it a very promising material for use.

5.3.1. Antibacterial activity

The success of dental implant restorations is between 95 and 98 % [27]. Surgical trauma, occlusal overload and bacterial infection are amongst the few important causes of implant failure. The main reasons for peri implant infection is bacterial colonization [45]. In scenarios where the soft tissue seal is not proper, the implant abutment gets exposed to the oral environment. On exposure to oral environment, a peri implant biofilm is formed within minutes. This over the course of days and weeks, get transformed into complex multispecies communities. Irrespective of the care taken during the manufacturing process to fabricate a polished surface, there always exists a micro gap between the soft tissue and the abutment which allows for the infiltration of bacteria. Thus, implant materials or coating which possess antimicrobial effect are a boon in such situations. It has been proven in literature that graphene coatings can also be used as antimicrobial coatings [46].

Graphene has proven its metal as antibacterial material. Rocha et al. [27], in the year 2023, functionalized the surface of titanium specimens with graphene oxide and copper oxide to assess their antimicrobial activity in lab. Their test consisted of four groups: G1 (Cu2O coating); G2 (GO coating); G3 (GO þ Cu2O coating) and G4 (no coating). After testing the antibacterial parameters, it was seen that the test sample with only graphene oxide had the most no of dead bacteria on its surface. In the year 2021, Jang et al. [47], worked on the antimicrobial action on zirconia implants coated with graphene oxide. In their study an atomic pressure plasma generator was used to coat the zirconia implants following which they were subjected to a series of tests of which crystal violet staining was conducted for evaluating the adhesion of streptococcus mutans. The results showed that the attachment of *S. mutans* was significantly reduced in the zirconia coated with graphene implants highlighting the antibacterial potential of graphene.

5.3.2. Drug delivery carrier

As we have seen so far throughout the text, the unique characteristics possessed by graphene and its derivatives have helped it gain a lot of trust and popularity in various fields including dentistry. Amongst graphene oxide and reduced graphene oxide, there has been extensive research on graphene oxide as it has expanded its scope of use to biomedical applications as well. Due to its large dosage loading capacity, excellent biocompatibility and low toxicity, GO has expanded its usage as a drug and gene delivery agent. Lately, there has been a need for administration of therapeutic proteins for tissue engineering. These therapeutic proteins, when administered into the body, disintegrate rapidly due to their short shelf life. As local drug delivery systems can release these agents over a prolonged period of time, the therapeutic efficacy of the agent gets enhanced.

To improve the process of osseointergration, dental implants made of titanium can be combined with therapeutic protein delivery systems. Though titanium implants do osseointegrate with bone, it does possess weak osteoinductivity and osteoconductivity. The administration of bone morphogenic protein-2 (BMP-2) can induce osteogenic differentiation which can further improve osteointegration. However, for effective bone formation there must be a long-term release of BMP-2. Therefore, W. G. La et al., carried out a study to investigate how effectively GO can carry and deliver the therapeutic protein for bone production to determine whether graphene may be employed as a possible carrier. In their work, the graphene oxide was deposited by the layer-by-layer (LbL) assembly of positively and negatively charged GO. The LbL technology allows us to prepare thin films with the desired functionalities with precise control over the composition, thickness, and electrostatics onto virtually any substrate. The interactions between the substrate and graphene is mediated through either electrostatic repulsion, hydrogen bonding or covalent bonding. Once graphene is coated onto the implants, BMP-2 was loaded onto the implants and tested to assess the extent of osteogenic differentiation of human bone marrow-derived mesenchymal stem cells. The results showed a clear difference between the amount of stem cells produced on graphene oxide coated implants to those of normal titanium implants. This was then followed by animal studies whose results again were in favor of graphene coated implants.

In the following year, i.e., 2014, W. G. La et., again performed another trial wherein they worked on similar materials. However, this time there was an addition in the form of substance P. A neuropeptide of 11 amino acids called Substance P (SP) plays a role in a variety of processes, including the control of inflammation, wound healing, and angiogenesis. Recent research has shown that SP encourages MSC recruitment and mobilisation into blood circulation. Thus, SP was co-delivered using Ti or GO-coated Ti to further promote bone formation in their study. The dual delivery of BMP-2 and SP using Go-coated titanium shoed greatest new bone formation when compared with the control group.

6. Conclusion

This review has highlighted the various applications of graphene in the field of implant dentistry. We have tried to classify the various actions under three broad categories namely physio-mechanical, Biomechanical and Pharmacological and mention in brief a few studies related to the same. Considering the various research done on the material, it can be seen that graphene does have a bright future in implant dentistry. However, as there is no end to gaining knowledge, there can be various aspects pertaining to graphene and dental implants which can be studied in greater depths to understand this relation better.

7. Limitations and future scope

The Limitations of the current review include.

7.1 Thought this article covers a wide range of properties, there are many more mechanical parameters such as fatigue strength, fracture strength, yield strength etc which need to be studied. Hence, furthu research in this field is going to be require.
7.2 There is no conclusive data on the ideal concentration of graphene that can be incorporated. Hence, more research in this area would be beneficial.
7.3 There is no conclusive evidence on the best method of incorporating graphene in dental implants. Hence, studies need to be carried out which would test between the different methods of graphene incorporation.

Data availability

Data will be made available on request.

CRediT authorship contribution statement

Rohan Yatindra Vaidya: Writing – review & editing, Writing – original draft, Investigation. **Aparna I.N:** Writing – review & editing, Methodology. **Dhanasekar Balakrishnan:** Writing – review & editing, Methodology. **Hidemi Nakata:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Karthik S:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Gayathri Krishnamoorthy:** Writing – review & editing, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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