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Applications of Graphene Composites in Bone Repair

Jiaxun Yu

College of Chemistry and Materials Science, Jinan University, Guangzhou 511443, Guangdong, China
yujx45@sina.com

ABSTRACT

In clinical orthopedics, the effective management of bone defects remains a major challenge. Conventional options—including autografts, allografts, and synthetic substitutes—are often limited by insufficient mechanical strength, weak osteoinductive capability, and poor antimicrobial performance. In contrast, graphene and its related derivatives possess a distinct two-dimensional architecture combined with outstanding mechanical strength, electrical conductivity, and biocompatibility, making them promising promising novel modifying agents for applications in bone tissue engineering. This review systematically summarizes the recent progress of graphene-based composites used in bone repair, with emphasis on their functional mechanisms serving as mechanical reinforcement frameworks, osteoinductive factors, electroactive interfaces, antibacterial barriers and immunomodulatory components. It summarizes application cases of graphene composites with matrix materials including hydroxyapatite, polylactic acid and chitosan, and highlights the advantages of such materials in repairing large-segment bone defects and infectious bone defects. Graphene-based composites can markedly enhance the mechanical strength of scaffolds, facilitate osteogenic differentiation and angiogenesis, and achieve synergistic antibacterial and anti-inflammatory effects, offering new strategies and material prospects for clinical bone repair.

KEYWORDS

Graphene; Bone repair; Tissue engineering scaffold; Osteogenic differentiation; Biocomposite materials

1. INTRODUCTION

The human skeleton provides essential mechanical support, and any disruption to its structural or functional integrity can impair normal physiological processes. Among the most persistent orthopedic challenges are large-segment bone defects arising from high-energy injuries, osteoporosis, surgical tumor removal, and other pathological conditions. According to existing epidemiological studies, the incidence of traumatic fractures in the Chinese population has been increasing annually, with rates of 2.50‰, 2.84‰, and 3.21‰ recorded from 2012 to 2014, respectively. In the United States, compared to 2 million fractures and $17 billion in medical expenses in 2005, both figures are expected to increase by 50% by 2025.

Graphene consists of a single layer of carbon atoms bonded via sp^2 hybridization, which arranges them into a two-dimensional hexagonal lattice resembling a honeycomb. This distinctive atomic arrangement gives rise to outstanding properties across multiple domains, including mechanics, thermotics, electronics, optics, and quantum behavior. In 2004, Geim and Novoselov successfully isolated single-layer graphene for the first time using a mechanical exfoliation method—a breakthrough later honored with the 2010 Nobel Prize in Physics. The present review concentrates on recent progress concerning graphene-based materials applied to bone repair.

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For the sake of clarity, all references to graphene-based materials and graphene and its derivatives in this paper collectively refer to pristine graphene, graphene oxide (GO), reduced graphene oxide (rGO), and their composite materials applied for bone repair.

2. THE USE OF GRAPHENE-BASED COMPOSITES IN BONE REPAIR APPLICATIONS

Contemporary bone repair strategies generally rely on three classes of materials. Autologous bone remains the clinical gold standard because of its outstanding biocompatibility, inherent osteoinductive and osteoconductive properties, and strong capacity to promote new bone formation. Allografts are primarily indicated for cartilage repair, especially in athletic populations, with reported 10-year survival rates between 78% and 91%. Synthetic alternatives fall into three subcategories: ceramic-based biomaterials such as hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP); and biodegradable polymers including polylactic acid (PLA) and polycaprolactone (PCL); and metallic implants, typically titanium and its alloys. Despite extensive clinical use, each type has inherent limitations, including insufficient elastic modulus, poor osteoinductive potential,and inadequate antibacterial efficacy.

2.1. As a Structural And Mechanically Reinforcing Framework

As typical two-dimensional nanomaterials, graphene oxide (GO) and reduced graphene oxide (rGO) exhibit outstanding mechanical performance. Their use as a reinforcing filler can markedly increase the matrix's mechanical strength and its physical attributes, thus fulfilling the load-bearing demands of bone tissue. A summary of mechanically reinforced graphene-based composites is provided in Table 1.

Both PLA and HA inherently possess moderate mechanical strength. In one study, Sharma and co-workers introduced polydopamine-reduced graphene oxide (PD-rGO) as a reinforcement, which substantially boosted the mechanical behavior of PLA-based scaffold materials [1]. The research group led by Oliveira fabricated a nanocomposite by hot-pressing a PLA matrix containing carbon nanotubes/graphene nanoribbons (GNR) together with nanohydroxyapatite (nHA). Within this composite, GNR served as a reinforcing phase that worked synergistically with nHA, leading to enhanced overall mechanical performance and structural integrity. Using a soft-templating technique, Zhou and colleagues constructed a hierarchically porous composite scaffold made of HA and rGO. This HA/rGO scaffold exhibited a fracture strength of 20.0 MPa—substantially higher than the 9.8 MPa measured for pure HA—thereby significantly improving biomechanical strength and structural stability, which makes it a promising candidate for repairing large segmental bone defects [2].

The addition of GO to collagen and collagen-apatite scaffolds significantly increases the elastic modulus; rGO modification leads to even better mechanical characteristics, thereby enhancing the scaffolds' compatibility with load-bearing conditions [3]. In PLGA and PMMA matrices, GO greatly improves both compressive strength and elastic modulus, serving as a core component for mechanical property enhancement, while other modifications show no significant synergistic effect [4]. Moreover, the use of graphene and its derivatives can increase the hardness, mechanical strength, and structural stability of multi-component composite hydrogels and scaffolds without compromising their highly porous nature [5, 6].

Table 1. Mechanically reinforced graphene-based composite materials

Material	Graphene and its derivatives attached	Functional features	Application	References
Hydroxyapatite	GO	No need for cells or growth factors; good osteogenesis and biocompatibility.	Craniofacial bone regeneration	Kim et al. (2024) [7]
	rGO	Boosts cell attachment, multiplication, and innate osteogenic differentiation; degradation rate matches new bone formation.	Accelerates repair of large segmental bone defects	Zhou et al. (2019) [2]
Chitosan	GO	Induces the osteogenic specification of bone marrow mesenchymal stem cells.	As a bioadhesive for bone tissue adhesion and repair	Saravanan et al. (2018) [5]
	graphene nanoplatelets	Excellent mechanical profile and bioactivity.	Utilized as bone tissue engineering scaffolds	Seifi et al. (2024) [6]
Collagen, Hydroxyapatite	GO	Enhances biomimetic mineralization ability; promotes both the proliferation of stem cells and their adoption of an osteogenic phenotype.	Localized bone defect healing	Fu et al. (2021) [4]
	rGO	High compressive modulus and outstanding mechanical characteristics. Induces BMSCs toward an osteogenic lineage.	Repairing bone	Norahan et al. (2019) [3]
Polylactic acid	GO	Promotes angiogenesis, osteogenic differentiation, and M2 polarization of macrophages (antibacterial); increases mechanical strength.	Artificial bone material	Xue et al. (2022) [8]
	rGO	Possesses multiple functions including antioxidant, pro-angiogenic, osteoinductive, and anti-biofilm properties.		Sharma et al. (2021) [1]
	Graphene nanoribbons	Good biocompatibility and low toxicity.		Oliveira et al. (2021) [9]

2.2. As a Bioactive Factor or Osteoinductive Factor

During bone regeneration and scaffold implantation, bone regeneration scaffolds need to possess both mechanical support properties and bioactivity to enhance osseointegration and osteogenic integrity. Table 2 lists the types of Multifunctional active composite materials.

When GO was incorporated into collagen- or gelatin-based apatite scaffolds, the unmodified control group showed only sparse cell attachment on the surface. In contrast, scaffolds containing 0.1% or 0.2% (w/v) GO promoted dense cell clustering. These observations suggest that GO can markedly boost biomimetic mineralization capacity, as well as enhance cell adhesion and osteogenic activity, thereby offering a valuable approach for improving bone repair scaffolds [10]. The role of GO-GelMA-Ap microgels is shown in Figure 1.

Yan and colleagues performed an in vivo study in which dental pulp stem cells were pre-activated with 10 nm graphene oxide quantum dots (GOQDs, 5 μg/mL) and then combined with a GelMA matrix. This construct effectively repaired cranial bone defects. Mechanistically, GOQDs trigger mitophagy, remove reactive oxygen species and damaged mitochondria, stabilize cellular energy homeostasis, and also ferry amorphous calcium ions to mineralizing sites. Through these dual functions, GOQDs enhance the osteogenic lineage commitment of stem cells [11].

The chitosan-GO composite system exhibits both pro-osteogenic differentiation and pro-angiogenesis effects. Osteogenic differentiation depends on the coordinated expression of Runx2 and genes including ALP, COL-1, and OC which serve as differentiation markers. The study by Saravanan and

colleagues demonstrated that GO-modified hydrogels can upregulate osteocalcin secretion and significantly augment the capacity of mesenchymal stem cells for osteogenic lineage commitment at the cellular level. A multifunctional nanocomposite composed of the hybrid system composed of quaternized chitosan, GO, and polydopamine (hereinafter QCS-GO-PDA) significantly enhances the tube-forming ability of endothelial cells, promotes more cells to enter the proliferative S phase, and is also the composite system with the best pro-osteogenic differentiation effect, according to Xue et al. [8].

Table 2. Multifunctional active composite materials

Material	Graphene and its derivatives attached	Functional features	Application	References	References
Alginate	Highly oxidized graphitic carbon nitride (Ox-gCN)	Rapid hemostasis, antibacterial, pro-coagulant, and osteogenic properties	Traumatic bone injury repair	Dutta et al. (2025) [12]	[2]
	GO	Biomimetic extracellular matrix structure; enhances both osteogenesis and angiogenesis	Bone regeneration	Yang et al. (2026) [13]	[3]
Gelatin Methacryloyl	GO	It possesses non-swelling, conductive and photothermal antibacterial properties, as well as excellent osteogenic, angiogenic and anti-inflammatory performances	Boosted biomimetic mineralization and in situ bone restoration	Li et al. (2022) [14]	[5][6][7] [8]
Tricalcium phosphate, gelatin, chitosan	rGO	Good photothermal effect, antibacterial properties, and biocompatibility; improves hydrophilicity and mechanical strength	Bone repair	Cabral et al. (2024) [15]	[4]
Polycaprolactone	GO	Electro-responsive activity; promotes cell proliferation and reduces immune response	Skull defect repair	Wang et al. (2019) [16]	[9]
Gelatin	GO	High adhesion; promotes BMSC osteogenesis	Repairing bone defects	Peng et al. (2023) [10]	[10]
Graphene oxide quantum dots		induce osteogenic differentiation in DPSCs by controlling mitophagy	Bone regeneration	Yan et al. (2017) [11]	Yan et al. (2017) [11]

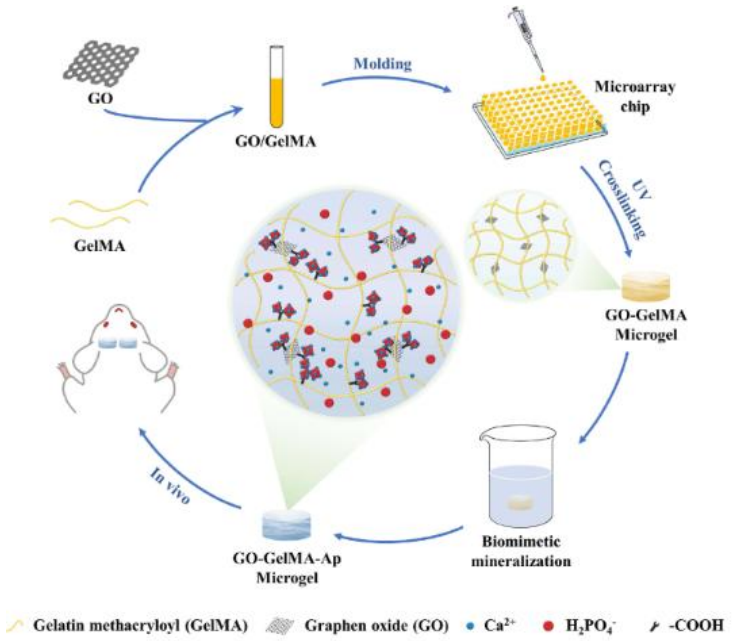


Figure 1. Schematic illustration depicting the preparation procedure of GO–GelMA-Ap microgels and their use in repairing cranial bone defects. [10]

2.3. As an Electroactive Interface And Antibacterial Barrier

The electrical conductivity and many other biological properties of graphene give it the potential to serve as an electroactive interface, an antibacterial barrier, and to perform more specialized functions.

According to Li and associates, graphene-based materials have great potential as scaffolds for transmitting microcurrents and bioelectrical signals within the human body [14]. PCL itself can be used as a bone repair scaffold, but it lacks electrical conductivity. Wang and his team carried out the first study on the effect of 3D printed PCL/graphene scaffolds coupled with electrical stimulation for bone regeneration [16]. Seifi et al. observed that a homogeneous dispersion of graphene-carbon nanotubes along with silver nanoparticles created a three-dimensional conductive architecture. This network was capable of efficiently conducting electrical signals and modulating the activity of osteoblasts seeded onto the scaffold [6]. These results collectively indicate that simultaneously employing graphene-containing electroactive interface scaffolds and electrical stimulation (microcurrent therapy) in vivo can hasten the bone healing process at cellular and molecular scales, as well as regulate bone remodeling, which represents a promising approach to encourage new tissue growth.

Graphene-based materials exert antibacterial effects through two principal pathways. The first is a physical barrier mechanism that impedes bacterial attachment and migration. Although the dense two-dimensional structure of graphene limits permeability, this can be adjusted when the material is incorporated into porous scaffolds, thereby achieving antibacterial action. The second pathway relies on nanoparticle-induced oxidative stress and charge transfer. A barrier membrane made of multilayered graphene hydrogel (MGH) employed for guided bone regeneration (GBR), can completely block cell passage while allowing liquids and small nutrient molecules to enter the tissue. Sun et al. developed a 3D printed highly adhesive artificial periosteum that can guide bone cells to preferentially grow into the defect area [17] (see Figure 2). Both types of membranes can isolate the entry of external contaminants such as bacteria, establishing a conducive microenvironment for bone healing. The latter mechanism is chemical. Seifi et al. compared the diameters of inhibition zones before and after adding silver nanoparticles and carbon nanotube composites, demonstrating that composite systems containing carbon nanotubes and silver nanoparticles have high antibacterial application potential in the modification of bone repair materials [6]. Two different hydrogels and a 3D printed composite scaffold containing either oxidized graphitic carbon nitride (Ox-gCN) or GO both promoted the generation of O2 and •OH free radicals, thereby accelerating the accumulation of reactive oxygen species (ROS) and leading to bacterial degradation, inducing ROS accumulation inside bacterial cells and modulating the membrane potential on the bacterial cell surface, thus effectively eliminating bacteria [12].

Furthermore, graphene-based materials exhibit broad and intense absorption of near-infrared (NIR) light. When scaffolds are combined with NIR light therapy, they generate a photothermal effect, which helps accelerate bone regeneration and also possesses antibacterial properties. The study by Cabral et al. showed that the photothermal effect exhibited by the scaffolds correlates with the amount of rGO incorporated into their structure, and the antibacterial effect becomes more pronounced at higher temperatures [15].

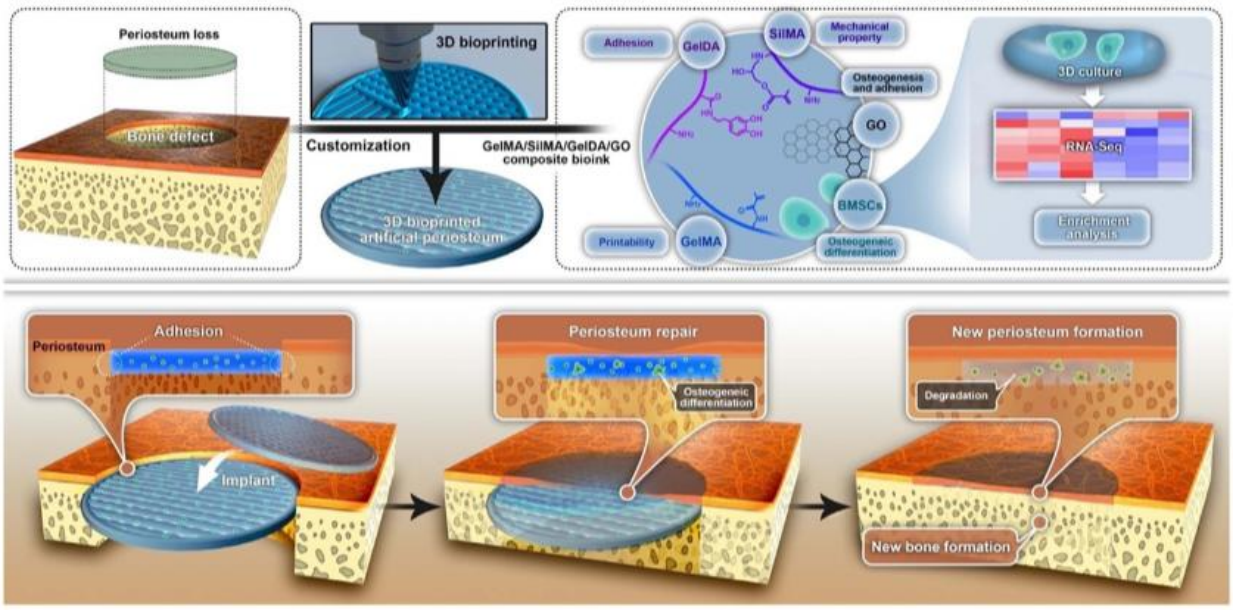


Figure 2. A 3D bioprinted biomimetic woven periosteum possessing strong adhesion and osteogenic capability was fabricated using a GelMA/SilMA/GelDA/GO BMSC-loaded composite bioink. The strong adhesion between this biomaterial and host tissue arises primarily from GelDA and GO nanosheets. This 3D printed artificial periosteum significantly enhances the generation of fresh periosteum and newly formed bone within the bone defect region. [17]

2.4. Immunomodulatory and Anti-Inflammatory Functions

Although graphene itself does not possess the function of maintaining immune system homeostasis, when combined with certain biomaterial scaffolds or bone repair materials, it can exhibit good anti-inflammatory properties and effectively regulate the immune environment.

A crucial step in immunomodulation is the increase in M2 macrophage numbers and the induction of macrophage polarization toward the M2 phenotype. Multiple studies have indicated that graphene-based materials, particularly graphene oxide (GO), can act as immunomodulators that regulate the polarization state of macrophages. Similar conclusions were drawn in a study by Xue and colleagues using a composite of quaternized chitosan, GO, and polydopamine (QCS-GO-PDA) [8]. CD206 immunofluorescence staining revealed that the QCS-GO-PDA group exhibited the highest fluorescence intensity and the highest CD206 expression level compared with the QCS and QCS-GO groups, indicating the strongest ability to promote the phenotypic switch of macrophages to M2.

A further mechanism for alleviating the inflammatory response is the inhibition of inflammatory cytokines and the suppression of macrophage activity. The presence of exogenous materials typically causes upregulation of major pro-inflammatory cytokines such as TNFα and IL-1β. Dutta and colleagues conducted qRT-PCR (quantitative real-time reverse-transcription polymerase chain reaction) to evaluate inflammatory factor expression. Their findings demonstrated that when cells were exposed to alginate/gelatin scaffolds containing Ox-g-CN, the mRNA levels of pro-inflammatory cytokines, including IL-6 and TNFα, fell by 4- to 5-fold [12]. Similarly, Wang et al. reported that the inflammatory response triggered by PCL and PCL/graphene composite scaffolds was much milder than that of clinically used suture materials, with lower levels of TNFα and IL-1β, indicating that these scaffolds do not stimulate an inflammatory response. Furthermore, by lowering reactive oxygen species (ROS) levels in macrophages, QCS-GO-PDA lessened the severity of the inflammatory response during tissue repair and fostered regeneration [8]. Collectively, these studies demonstrate that GO can enhance the immunomodulatory capacity and anti-inflammatory properties of composite materials, suggesting promising application prospects in this field.

3. CONCLUSION

In summary, graphene and its derivatives can be incorporated into bone repair materials to fulfill multiple roles: (i) a structural and mechanical reinforcement; (ii) a bioactive/osteoinductive agent; (iii) an electroactive interface and antibacterial barrier; and (iv) an immunomodulatory/anti-inflammatory component.

Because of its wide range of distinctive biological properties, graphene has emerged as a significant focus in bone and cartilage tissue engineering and also offers potential for achieving novel clinical advances. Nevertheless, despite more than a decade of research and initial evidence supporting its effectiveness in bone repair materials, the precise mechanisms by which graphene interacts with different cells, tissues, and organs remain to be fully elucidated.

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