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Review Article

# Graphene-based materials for bone tissue engineering

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## ABSTRACT

Bone is capable of regenerating itself when it suffers minor injuries. However, treatment of bone that does not regenerate due to major injuries usually requires a surgical application. On the other hand, tissue engineering aims to eliminate problems such as lack of donor tissue and incompatibility that occur in these surgical interventions. Scaffolds are the most important structure produced to fulfill this goal of tissue engineering. Scaffolds provide an environment for cell attachment, proliferation, and differentiation, thereby helping to form new tissue. Some properties such as mechanical properties, surface properties, biodegradability, biocompatibility, and porosity should be considered during the designing of the scaffold. The creation of the scaffold for the determined tissue is related to both the materials used and the production methods. The use of graphene and its derivatives in scaffolds are one of the important applications in tissue engineering as a regulator for cell proliferation and differentiation. Graphene (Gr) and its derivatives have a significant role in bone regeneration thanks to their mechanical and biological properties when used in bone tissue engineering applications. This study reports the importance and advantages of using graphene-based biomaterials in scaffolds for bone tissue engineering. The biological properties of graphene-based biomaterials obtained in various studies have improved and there has been an increase in the adhesion and proliferation of osteoblasts.

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## INTRODUCTION

Tissue engineering is an interdisciplinary field that provides the repair and restoration of the structure and functions of living tissues or organs and works with departments such as biology, materials engineering, medicine, and chemistry for this purpose [1]. Cells, scaffolds, nanoparticles, proteins, signal-transmitting molecules are the most important elements in tissue engineering applications. The tissue engineering method includes tissue support that protects and supports cell attachment and functionality, a rich source of cells selected in accordance with the target tissue, and growth factors or cellular signals that control the behavior of these cells [2]. Tissue engineering studies have increased with the increasing demand for organ and tissue transplants.

Tissue transplantation with traditional methods brought along immunological problems and time loss. In

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order to eliminate these problems, it is aimed to reduce the waiting time of patients for organ transplantation to produce tissues compatible with the patient, and to eliminate the risk of inflammation, together with tissue engineering studies [3].

In tissue engineering, scaffolds act as the matrix for cell attachment, proliferation, and differentiation and require sufficient mechanical strength to carry [1]. Biologically, the extracellular matrix (ECM) is the structure that supports the development and cell formation. Permeability, which is an important factor in the scaffolds, helps to allow the transfer of nutrients necessary for the cell and to remove the resulting metabolic wastes from the environment without creating a toxic effect. At the same time, when the scaffold is replaced by cells, the scaffold must be degraded and removed from the body without producing toxic substances. Mechanically, scaffolds help withstand external pressures and give structural support to the tissue to be regenerated [4].

The graphene family consists of various derivatives such as graphene oxide (GO), reduced graphene oxide (rGO), graphene quantum dots (GQDs), graphene nanosheets, single-layer graphene, and several-layer graphene [4]. Graphene-based scaffolds are a special class of scaffolds composed of Gr, GO, and/or rGO nanocomposites, and it will be examined this class in this review. Although there are many nanomaterials, graphene and its derivatives are attractive candidates for developing tissue engineering scaffolds thanks to their tunable electrical conductivity, excellent mechanical properties, biocompatibility, chemically changeable surfaces, compatible cell surfaces receptors and similarity to ECM [5]. Graphene's large surface area, excellent carrying properties, and the strongest material with 130 GPa make it one of the most important components for a scaffold. In this way, the addition of Gr and its derivatives to polymeric scaffolds increases the mechanical properties, toughness, and tensile strength of the scaffold. Consequently, graphene-based scaffolds can be used to mimic and regenerate tissues, as well as accelerate cell repair and wound healing during bone repair [6]. Gr, GO, and rGO improve the physicochemical properties and bioactivity of biomaterials [7]. Gr, GO and rGO are used as ideal agents in tissue engineering applications because of all these attractive properties (Figure 1).

## GRAPHENE AND GRAPHENE-BASED MATERIALS

Graphene consists of sp2 hybridized carbon atoms and is a two-dimensional nanomaterial. Graphene can be coiled, folded, and stacked and three-dimensional graphite, one-dimensional nanotubes, and zero-dimensional fullerene can be formed thanks to these forms.

Graphene has excellent properties such as good optical properties, a large surface area, [5,8] high mechanical properties [9], superior thermal conductivity [10,11], and barrier properties [12]. The flexibility of the bonds of carbon atoms to each other is related to the properties of graphene. The strength of graphene with 130 GPa makes it the strongest material in the world [13]. The structural stability of graphene is maintained due to the warping of the plane of the carbon atom. The high surface area of graphene increases its facility to absorb and to bind more loads. Graphene has high

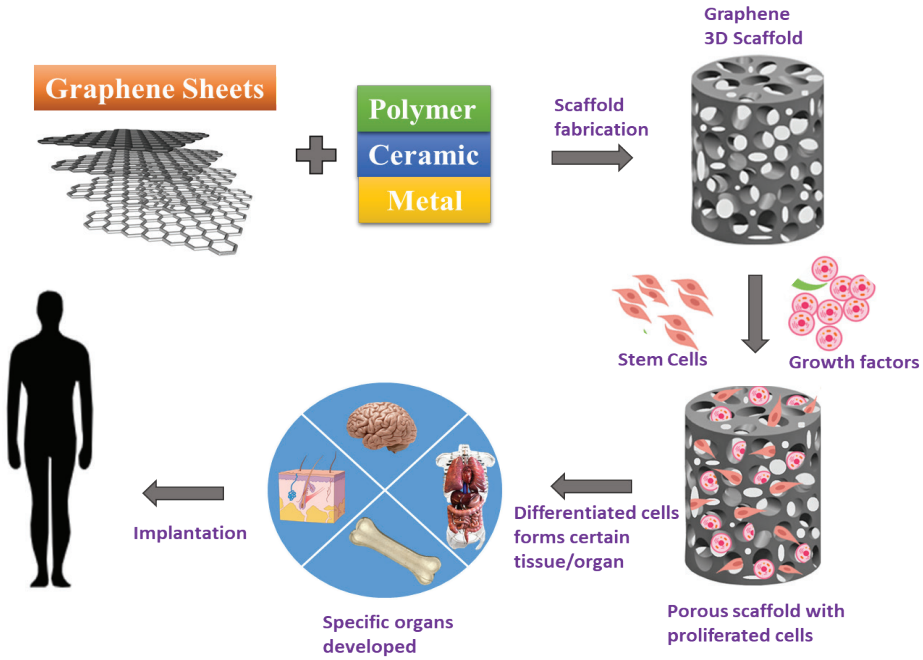


**Figure 1.** Schematic diagram of graphene 3D scaffolds in tissue engineering.

electrical conductivity which is supplied by electron mobility [14]. Graphene is actively used in applications of disease diagnosis, cancer treatment, biosensors, bioimaging, drug, and gene delivery. It shows very good biocompatibility due to the surface properties of graphene [9].

GO has oxygen-containing functional groups that can bind to biomolecules. These functional groups are epoxy, hydroxyl, carboxyl, and carbonyl [15]. Increasing the diffusion of graphene into the matrix phases and reducing the phase separation and accumulation of graphene can be achieved by these oxidized functional groups of graphene oxide. These functional groups show better mechanical, biocompatibility, and bioactivity properties in bioapplications. Also, they allow graphene oxide to form a strong interfacial bond between filler and matrix [16]. Graphene oxide contains both hydrophobic and hydrophilic regions thanks to its amphiphilic feature [17]. The hydrophobic region attracts drugs, genes, or other molecules by electrostatic attraction. The hydrophilic zone allows the functionalization of graphene oxide. Hydroxyl and carboxyl functional groups acquire better hydrophilicity to graphene oxide than graphene. GO is obtained by the oxidation of graphene [18].

Graphene oxide that contains different oxygen groups can be reduced physical or chemical to obtain rGO. rGO can be gained by using to prepare graphene sheets. The general properties of the reduced graphene oxide, which is formed by the loss of oxygen-containing groups as a result of the reduction reaction of graphene oxide, are very similar to graphene nanolayers [19]. Reduced graphene oxide has good electrical properties thanks to the cost-effective method. There are some different strategies such as chemical reduction, photo-reduction, microwave-assisted reduction, solvothermal reduction, and thermal reduction which are used in order to reduce graphene oxide. Graphene can significantly increase the mechanical properties [20], elasticity [21], and flexibility of the material which it be contained.

Pristine graphene increases osteogenic differentiation and aids in both cell attachment and proliferation. In addition, GO and rGO improve the physicochemical facilities and bioactivity of biomaterials as in pristine graphene. This is because graphene oxide is highly hydrophilic and its surface carries carboxyl, epoxy, and hydroxyl groups. In addition, these groups provide the interfacial interaction between the GO and the material [22]. So, graphene, GO and rGO are very useful to combine with materials such as metal, ceramic, and polymer to obtain composite materials.

Graphene-based materials have high surface areas, distinct surface properties, excellent mechanical strength and hardness, high biocompatibility, good electrical conductivity, pH sensitivity, and a variety of two-dimensional (2D) and three-dimensional (3D) morphologies [23]. In order to fabricate new delivery systems, materials that are called graphene-based nanomaterials can be formed by using together GO and rGO with drugs, genes, photosensitizers, and other cargos materials. These materials are fabricated to use in phototherapy and multimodality therapy applications in tissue engineering that is including bone, cartilage, neural, skin/adipose, cardiac, and musculoskeletal tissue engineering [24]. Moreover, graphene-based materials are used in many areas such as gene delivery, gene therapy, bioimaging, biosensor, and biomedical. And also, these materials are used in drug delivery applications (Figure 2). The reasons for using graphene-based composites for applications of drug delivery are to pass to cell membranes well and to have a high surface area that ensures many attachment regions to a target of the drug. These materials are useful materials for enhancing cell growth and differentiation. When using graphene for drug

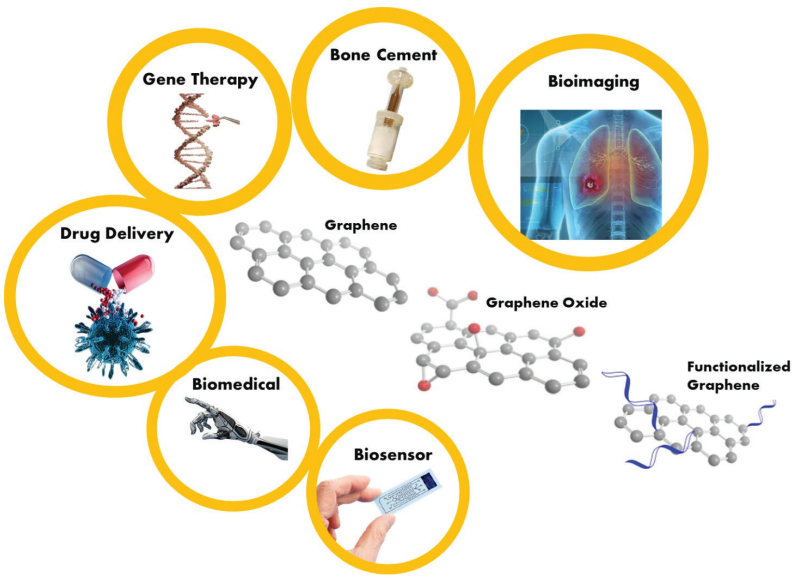


**Figure 2.** The application areas of graphene and graphene-based materials

delivery, it can induce drugs non-covalently via many interactions such as hydrogen bond interaction and hydrophobic interaction [25]. Bioimaging helps to observe and examine biological operations from the subcellular to the small animal level. Bioimaging provides both on researching bioimaging and on clinical practices. When suitable prob uses for bioimaging, it can determine early-stage diseases and observe the treatment response. Graphene can be becoming to an ideal agent that is combined with small molecules such as dyes, fluorescent nanoparticles, or biomolecules to improve their luminescent properties for bioimaging applications [26-28].

## SYNTHESIS OF GRAPHENE

Graphene can be fabricated by three methods which are mechanical exfoliation/cleavage, chemical vapor deposition, and chemical-based. The number of layers of graphite sheets is a very important parameter for the properties of graphene [29].

**Mechanical Exfoliation/Cleavage**

Graphite consists of graphene sheets that are held by Van der Waals interactions. The method of exfoliation is used to break these weak interactions between the graphene sheets. Separating the graphene layers individually provides for exploiting of excellent properties of graphene [30]. Exfoliation is involved many techniques such as liquid-phase exfoliation, mechanical exfoliation, exfoliation of GO, and more [29].

**Chemical Vapor Deposition**

Chemical vapor deposition is one of the most useful techniques to produce graphene with a single or few layers. This method requires a metallic catalyst. Hydrocarbons that are on the surface of this catalyst can synthesize graphene by decomposition of catalytic or graphite targets. The advantage of this method is that there are low or no metallic residuals. [31].

Also, heteroatom-doped graphene nanostructures can be synthesized by this method. For the aim of improvement of its productivity in applications of enzymatic and catalytic, bio-detection and energy conversion, it can be used nitrogen, phosphorous, sulfur, fluorine, brome, iodine to obtain functionalized graphene [32].

**Hummer's Method**

Graphene and its derivatives are generally synthesized by chemical-based methods. It is one of the most productive methods. Hummer's method is the most widely used method among chemical-based methods. In this method, Graphite is used as a carbon precursor, and it is oxidized in sulfuric acid in the presence of Potassium manganate (VII) ($KMnO_4$) as an oxidant. When the reaction reaches a certain temperature, the graphene oxide layers are separated by adding oxygen peroxide and water. Then it is washed with hydrochloric acid and water. Large amounts of graphene can be produced by using chemical-based methods [33,34].

## GRAPHENE-BASED COMPOSITES AND THEIR APPLICATIONS

One of the most important properties of graphene is that it has a large specific surface area. The interaction between graphene and many chemical compounds or biological species occurs thanks to this property of graphene. Also, the oxygen functional groups that are contained in GO and rGO make it easier to attach to molecules or biomolecules according to graphene. Graphene and its derivatives interactions with polymer, ceramic, and metal materials provide many facilities to materials such as mechanical strength, biocompatibility, etc. It is widely used in tissue engineering thanks to all these facilities of graphene-based materials.

## GRAPHENE-BASED POLYMER COMPOSITES AND THEIR APPLICATIONS

Recently, the use of graphene-based polymeric materials has been increasing because of the advantages of graphene-based polymer matrix composites. These advantages include improving the electrical/mechanical properties of graphene-based polymer materials as well as improving their biocompatibility properties [35].

In addition, graphene-based polymer materials provide controllability in pore size, porosity, and pore distribution of scaffold structure for getting better bioactivity in scaffold production. Graphene-based polymer composites are widely used in both soft and hard tissue engineering application areas. This is because graphene-based polymer materials are flexible materials with good mechanical properties. The good electrical conductivity of graphene determines the cell signal response in situ in biosensors and living bodies [36].

The various processes such as melt blending, solution intercalation, sandwich making, and also covalent or non-covalent bonded processes like an in situ polymerization are used to prepare graphene-based polymer materials [37]. These preparation methods can be used alone or multiple methods together to prepare polymer /graphene composites [38].

Thermoplastic nanocomposites are simply prepared for large-scale industrial production by solvent-free melt compounding technique. Graphene and its derivatives can be mixed directly with the thermoplastic polymer melt in solvent-free melt compounding technique [39].

Many graphene-based polymer nanocomposites can be fabricated by in-situ polymerization. These nanocomposites are polystyrene (PS) /graphene [40], poly (methyl methacrylate) (PMMA) /expanded graphite [41], nylon-6 /graphene [42] and poly (vinylidene fluoride) (PVDF) /poly (methyl methacrylate) (PMMA) /graphene [43] etc. However, using the in-situ polymerization method to disperse nanoparticles into polymers is not as economical and scalable as the solution or melt compounding method [44].

Vernardou et al. reported that polylactic acid (PLA) / graphene conductive polymer composites are prepared well via fused deposition modeling. Graphene oxide has been

found not only to significantly increase mechanical properties but also to benefit cell proliferation [45]. Another study is the manufacturing of PLA/GO nanocomposite scaffolds. PLA/GO nanocomposite becomes a suitable material with its good antibacterial activity and biocompatibility for tissue engineering [46].

PLA and polyurethane (PU) are biocompatible and biodegradable polymers. The addition of graphene oxide to PLA/PU, which is a polymer composite does not interfere with normal human cell proliferation and differentiation. This addition shows a remarkable improvement in antibacterial capacity [47].

The addition of graphene oxide to the tricalcium phosphate (TCP) /PLA mix has resulted in a porous structure of the scaffold and increased cellular responses. This composite structure also shows a better swelling profile, improved biomineralization capacity, and better alkaline phosphatase (ALP) activity, and this structure show to be stronger than human cancellous bone [12]. Graphene oxide /TCP / alginic acid is used to produce bone scaffolds, which allow the nutrient exchange. The high porosity of the scaffold is increased with the addition of graphene oxide without changing the mechanical properties of the bone scaffold.

In addition, reduced graphene oxide can form nanocomposites with Polyester. The formed reduced graphene oxide-based polyester nanocomposites offer excellent antibacterial activity against cells. At the same time, PE/rGO has many facilities such as good mechanical strength, electrical property, thermal stability, and antibacterial capacity [48].

Polycaprolactone (PCL) is a biodegradable polymer, and it has a variety of biomedical applications such as sutures, subcutaneous contraceptive devices, and wound dressings. However, it has poor mechanical performance, which limits the use of polycaprolactone in orthopedic applications. Polycaprolactone is combined with graphene oxide and its derivatives to improve bioactivity, mechanical properties, and chemical interactions of composite. The modulus of elasticity of the composites can be increased by adding graphene to polycaprolactone. All modified polycaprolactone scaffolds allow cells to attach and proliferate [49].

Polyvinyl alcohol (PVA) and graphene oxide biocomposite scaffolds allow cells to attach and grow on the scaffold without affecting the viability of the cells. Cells are attached to scaffolds and grow on these scaffolds, which are nanofibrous biocomposite scaffolds of polyvinyl alcohol and graphene oxide, without affecting their viability.

In addition, the use of polydopamine functionalized reduced graphene oxide (RGOPDA) composite positively affects cell proliferation, adhesion, and osteogenic differentiation [50,51].

Chitosan (CHI) is a convenient biocompatible and biodegradable biopolymer to combine with graphene, GO, and rGO for applications of bone tissue engineering. The chitosan scaffold engineered with graphene oxide (CHI-GO scaffold) offers a higher serum albumin protein adsorption compared to the CHI scaffold [52]. At the same time, the interaction of the protein with its functional groups occurs, as the negative charge and polarity allow Electrostatic forces and Van der Waals forces. These properties are developed the binding and proliferation of preosteoblast cells in chitosan scaffold engineered with graphene oxide [53], osteoblast can support cell adhesion, proliferation, and bone matrix formation. It has been observed improvements in good mechanical properties and surface pores with the addition of graphene oxide [54,55].

Gene therapy is a method to treat genetic diseases with using genes. The important issue in that is to achieve effective and reliable vectors, which can keep DNA from the degradation of nuclease and enable its uptake with high transfection efficiency [56][57]. Graphene materials with high loading efficiency and gene transfection are suitable materials in gene delivery applications. Graphene and its derivatives are combined with polymers such as polyamidoamine [58], polyethyleneimine (PEI) [59], chitosan [60] to reduce cytotoxicity and achieve a cationic surface. The obtained cationic surface provides the interaction of graphene-based polymer composites with anionic molecules electrostatically. Liu et al. showed that using PEI with GO is suitable for gene delivery thanks to its low cytotoxicity and high transfection of gene delivery vector [61]. In the other work, Chen et al. used a poly(ethylenimine)-graphene oxide (PEI-GO) as a carrier to provide the transfection of the DNA plasmid into HeLa cells. The proton-sponge effect facilities to the development of transfection of PEI-GO [62].

Yang et al. found that graphene oxide is combined with poly (ethylene glycol) to use for bioimaging. The imaging can be speedily in living cells that have graphene oxide thanks to this material. This experiment offers many opportunities to use GO in bioimaging [26].

The surface polarity of graphite promotes the adsorption of proteins. This helps to increase the bioactivity of polymer-based biomaterials. In this way, graphene-based materials are frequently used in bioimaging applications [61]. In addition, the increase of surface roughness is supported by adding reduced graphene oxide into the polymeric scaffolds. The increased surface roughness allows the spreading and differentiation of cells with osteogenic potential. In summary, adding graphene to polymeric materials helps improve many properties of the polymers [62].

## GRAPHENE-BASED CERAMIC COMPOSITES AND THEIR APPLICATIONS

Bioceramics are biocompatible ceramic or glassy materials. They usually show great tissue compatibility [63,64]. However, these ceramic materials lack sufficient mechanical strength and osteoconductivity. To overcome this difficulty, the ceramic materials are combined with graphene oxide. Graphene can help to increase the mineralization of hydroxyapatite (HA) ceramics. It encourages to proliferate osteoblasts and to increase their activity. On the other hand, in vivo studies prove that the adding of graphene

into ceramic materials has not any negative effects on the organic microenvironment [65,66]. Therefore, the incorporation of graphene into ceramic materials, which are generally bioactive, develops their mechanical properties while preserving their natural biological properties. Some reinforcing mechanisms involve such as rack bridging, crack deflection, pull-out effect, tip shielding, grain-bridging, and refinement when using of graphene in ceramics [67]. The properties of composites that are composed of graphene and ceramic can vary according to the weight percentage of added graphene. The quality of graphene, the distribution of graphene nanolayers in the ceramic matrix, and the holding of the graphene at high temperatures for sintering also change the properties of the formed composite [68]. It is important that the distribution of graphene in a ceramic matrix during preparation of graphene ceramic composites such as akermanite /graphene [69], aluminum oxide /graphene [70], silicon dioxide /graphene [71], silicon carbide /graphene [72] and titanium carbide /graphene [73]. These composites with several matrix materials can include alumina, silicon nitride, zirconia, and silica, which are generally formed by powder processing.

The low fracture toughness of hydroxyapatite makes it very brittle and difficult to shape. Hydroxyapatite, which is bioceramic, is combined with graphene oxide to form a composite material. When the formed material is used in scaffold and coating, it gives enhanced capabilities to them. GO/HA composite coatings showed higher corrosion resistance compared to coatings made with pure hydroxyapatite. When GO/HA composite coatings are compared with coatings made with pure hydroxyapatite, GO/HA composite coatings showed higher corrosion resistance. The combination of HA and rGO shows improvement in their mechanical properties. At the same time, this combination provides the material with improved bioactivity properties [74].

Bioceramics are combined with graphene to form composites in order to eliminate low fracture toughness and fragile properties of bioceramics. Thus, graphene oxide combined with hydroxyapatite and tricalcium phosphate improves the ability to form bone that is called osteoconductive and accelerates to proliferate and differentiate osteoblasts [75]. Hydroxyapatite and tricalcium phosphate that are derivatives of calcium phosphate are used in the fabrication of scaffold for bone regeneration due to their high biocompatibility and osteoconductivity. Because of these properties, hydroxyapatite and tricalcium phosphate are used in the fabrication of scaffolds to regenerate bone [76].

Bioactive glasses are biomaterials that are surface reactive. They help to improve the osteogenic differentiation and revive the bone. Bioactive glasses can be combined with graphene oxide to enhance the mechanical characteristics of biomaterial. Therefore, it can increase the compressive strength and fracture toughness of the formed GO-bioglass scaffold [77]. Polymer-based scaffolds are used in bone tissue engineering as they aid in the growth and differentiation of cells in tissue. However, these scaffolds are not preferred to be used in load-bearing areas due to the insufficient mechanical properties of polymer-based scaffolds [78]. Hydroxyapatite is included in bone structure as an inorganic component, which is preferred by osteogenic cells to differentiate. The combination of hydroxyapatite and graphene gives polymers superior performance in promoting cell proliferation [4].

On the other hand, graphene layers have bound each other with strong van der Waals bonds. These strong interactions make it difficult to obtaining of the uniform distribution of graphene in the matrix. The irregular combination of graphene can affect the performance of composite ceramics [79].

## GRAPHENE-BASED METAL AND METAL OXIDE COMPOSITES AND THEIR APPLICATIONS

Metal matrix composites are generally used in applications due to their good performance in many properties such as mechanical strength, thermal conductivity, and electrical conductivity. When graphene-based metal composites are compared with pure metallic materials, they display better strength and Young's modulus. Some techniques such as mechanical mixing, chemical synthesis, electro-deposition, and self-assembly are used to form graphene-based metal composites [80]. The graphene and metal are mixed by the mechanical mixing method, which requires physical force [81]. Chemical synthesis methods, including in-situ synthesis, hydrothermal preparation, and molecular-level mixing, are used to prepare nanocomposites with reducing GO and metal salts [82,83]. The most known metals such as titanium, zinc, and silver can be combined with graphene and its derivatives [84]. Graphene-zinc oxide composite is obtained as a result of depositing zinc (II) ions or zinc oxide nanoparticles on graphene nanosheet surfaces. This composite exhibits superior antimicrobial effects [85,86]. The titanium dioxide ($TiO_2$) nanoparticle shows good antimicrobial properties when used with graphene oxide. The production of hydroxyl radicals at high speed by photocatalytic reaction increases the antibacterial activity of GO/$TiO_2$ [87,88].

Silver (Ag) nanoparticles are deposited on reduced graphene oxide surfaces to form nanohybrid materials. The obtained nanohybrids provide excellent antibacterial activity against *E. coli* owned by Ag/rGO. The synergic effects of the adsorption property of rGO nanosheets and the bactericidal property of silver nanoparticles give a good antibacterial property to Ag/rGO composite material [89]. Zhao and co-workers reported that synthesize of GO-Gold composite enhances not only intracellular bioimaging but also drug delivery carriers [90].Graphene composite biomaterials are used in various bioimaging applications like an optical imaging [91].

The graphene is composed with polymer, ceramic, and metal to obtain functional materials. Graphene-based composites are widely used in biological areas such as tissue engineering, drug delivery, gene delivery bioimaging, etc. Some of these applications are shown in Table 1.

**Table 1.** Graphene-based composites and their applications

| COMPOSITE | PRODUCTION | EFFECTS | APPLICATIONS | REFERENCE |
|---|---|---|---|---|
| PLA/GO | fused deposition modeling | increase mechanical properties, benefit cell proliferation | tissue engineering | [46] |
| PLA/PU | - | remarkable improvement in antibacterial capacity | tissue engineering | [48] |
| TCP/PLA | - | showing swelling profile, improved biomineralization capacity, and alkaline phosphatase (ALP) activity | tissue engineering | [49] |
| PE/rGO | - | high mechanical strength, thermal stability, electrical property, and antibacterial capacity | tissue engineering | [47] |
| Gr-ZnO | depositing zinc oxide on graphene nanosheet surfaces | exhibit superior antimicrobial effects | tissue engineering | [84] [85] |
| Sr/PCL/RGO | a gas foaming method | enhance to proliferate and differentiate osteoblast cells | scaffold for tissue engineering | [51] |
| BG-GNP | - | also increases the electrical conductivity | bone tissue engineering | [92] |
| GO- CHI-PCL-collagen | electrospinning | increased hydrophilicity, bioactivity of the scaffolds, and cell attachment and proliferation | scaffold for bone tissue engineering | [91] |
| CHI/PVA/GO | electrospinning | excellent mechanical properties of nanofibers; increased suitability of the environment for the growth of cells | scaffold for bone tissue engineering | [93] |
| PCL/Gr | 3D printing | improved hydrophilicity and biocompatibility<br>improved cell support<br>supporting neo-bone tissue formation | scaffold for bone tissue engineering | [94] |
| RGO/PDMS | a salt leaching method<br>Dip-coating | adipose-derived stem cells give improved efficiency in proliferation and osteogenic differentiation | scaffold for bone tissue engineering | [90] |
| GO/Car/HA | immersion-coating | better affinity to Ca ions, increases cell mineralization, and improved proliferation and osteogenesis | scaffold for bone tissue engineering | [52] |
| CHI/GO | freeze-drying method | increased mechanical properties and pore formation capability, improved bioactivity | scaffold for bone tissue engineering | [80] |
| HA/RGO | hydrothermal procedure | better cell affinity and biocompatibility | scaffold for bone tissue engineering | [65] |
| Gr/HA | 3D printing | upregulation of osteogenic gene expression | scaffold for bone tissue engineering | [95] |
| GO/PPy/HA | electrochemical deposition | good ability to revive osteoblastic cell proliferation | scaffold for bone tissue engineering | [96] |
| PLGA/HA/GO | freeze-drying method | high cell adhesion that revived proliferation and osteogenic differentiation | scaffold for bone tissue engineering | [97] |
| PCL/GO | electrospinning and coating | promoting differentiation into mature oligodendrocytes | neural tissue engineering | [98] |
| Gr/PAM | Freeze-drying | supporting hippocampal neurons and astrocytes improvement, developing synaptic networks | neural tissue engineering | [99] |
| GO-coated Ti6Al4V | coating | increasing of surface roughness and hydrophilicity, and supporting the adhesion, proliferation, and osteogenic differentiation of cells | coating for bone regeneration | [100] |
| GO-coated NiTi | coating | developed protein adsorption; the adhesion, spreading, proliferation, and osteogenic differentiation of preosteoblastic cells and give strong antibacterial activities | coating for bone regeneration | [82] |
| CHI/PVA/Gr | electrospinning method | rapid wound healing in mice and rabbits | wound healing application | [101] |
| PEI-GO | - | low cytotoxicity and gene delivery vector with good transfection efficiency | gene delivery | [102] |
| GO-Au | - | excellent antibacterial property | drug delivery | [26] |
| GO | - | imaging can be speedily in living cells | bioimaging | [29] |
| PVA/GO/$TiO_2$ | electrospinning and sol-gel reaction | increased tensile strength and elasticity modulus | environmental purification | [103] |

BG-GNP: Bioglass® with graphene nanoplatelets, Car: Carrageenan, CHI: Chitosan, Gr: Graphene, GO: Graphene oxide, HA: Hydroxyapatite, PAM: Polyacrylamide, PCL: Polycaprolactone, PDMS: Polydimethylsiloxane, PE: Polyester, PEG: Polyethylene glycol, PEI: Polyethylenimine, PLGA: Poly (lactic-co-glycolic acid), Ppy: Polypyrrole, PU: Polyurethane, PVA: Polyvinyl alcohol, RGO: Reduced graphene oxide, Sr: Strontium, TCP: Tricalcium phosphate, ZnO: Zinc oxide, $TiO_2$: Titanium dioxide

## GRAPHENE-BASED COMPOSITES IN TISSUE ENGINEERING APPLICATIONS

Tissue engineering can be defined as reconstructing and treating damaged tissues or organs using a scaffold. The conventional treatment brings about many problems such as donor deficiency, donor incompatibility, or post-transplant immunity. Tissue engineering gives new methods such as creating organs and tissues in the laboratory to remove these problems. Tissue engineering is associated with many fields such as engineering, medicine, and biology. Biomaterials provide some important cell parameters such as specific cellular functions, cell differentiation, and cell-cell interactions. Besides this, the most important properties of biomaterials are biocompatible and non-toxic.

Biomaterials are combined with graphene, or its derivatives and they can be used in many applications of tissue engineering. Graphene can be modified with some biomaterials such as protein, DNA, peptide, biopolymer, and enzyme to improve graphene applications areas. The addition of graphene and graphene oxide significantly increases the mechanical strength of biocomposites. In addition, composite materials formed with graphene and its derivatives enhance osteogenic differentiation [92,93].

Graphene-based materials are created by combining graphene with bioceramic, hydrogel, and bioactive glasses. Graphene does not damage the structure or biocompatibility of bioceramics, hydrogels, and bioactive glasses in the formation of these materials to improve their mechanical strength [94].

Cerruti et al. reported that the produced GO/HA hydrogel can be used in bone tissue engineering due to its important properties such as high porosity, excellent mechanical properties, high electrical conductivity, and good cell compatibility [65]. Another work is related to graphene oxide nanosheets with poly (acrylic acid) (PAA) /gelatin (Gel) hydrogels. It is shown that graphene oxide nanosheets can develop the mechanical properties of PAA /Gel hydrogels and CHI-hydrogel scaffolds [95].

Cheng et al. showed that the increase of neurite sprouting and cells growing on graphene substrates. According to obtained results, better neurite outgrowth is obtained by the high electrical conductivity of graphene and graphene can be used as an implant material or a neural chip in nervous system [96].

Graphene is used as a biomaterial in the nervous system in tissue engineering [97]. Also, graphene oxide can improve adipose tissue generation that helps to absorption of insulin. Graphene oxide is combined with gelatin for the biomimetic mineralization of hydroxyapatite. The obtained gelatin-functionalized graphene oxide (GO-Gel) support to adhere, proliferate, and osteogenic different of cell. GO-Gel is used as a scaffold that is able to promote osteogenesis for bone tissue engineering [98].

In addition, graphene chemical inertness and impermeability are other important properties. These properties allow graphene to be used as a biocompatible anticorrosion in the coating of metallic biomedical devices. Gr can be improved the biocompatibility of metal biomaterials. Li, M. et al. reported that GO/HA material coated by titanium. It has shown high corrosion resistance, excellent coating adhesion strength, and good cell viability [99]. Besides all the excellent facilities of graphene, it can be toxic when used in tissue. The toxicity of graphene is dependent on many parameters such as dose, concentration, and characteristics. Graphene-cell interactions can be changed according to the chemistry of surface, size or shape, and impurity of graphene. The chemistry of graphene surface is important to define cytotoxicity.

## BONE TISSUE ENGINEERING AND APPLICATIONS

Bone is the hardest of the tissues that make up the body and which acts as a support in the body. In addition to providing support to the body, it helps movement and protects internal organs [100]. In the traditional method, the damaged bone was treated autograft method (tissue taken from one area of the same person and transferred to another region) or allograft (tissue transfer between different people). Besides this, bone transplantation is taking place in conventional therapy; there is a risk of transmission of infectious diseases. In addition, the limited number of bones limits transplantation [101].

The functional bone implants produced do not carry any risk of infection or immunity in bone tissue engineering. Because of this reason, interest in bone tissue engineering works increases in the literature [100]. The obtained composite material can be developed chemical, physical, and mechanical properties compared to its single components [102]. Gr is a promising material for bone tissue engineering due to its unique physical, chemical, and mechanical properties. The commonly used materials are bioceramics, hydrogels, metals, polymers for tissue engineering scaffolds application areas. These materials can be significantly developed in their mechanical properties and stability by using graphene and GO as reinforcement materials [99].

### Stem Cell

Graphene, a biocompatible material, promotes stem cell growth and osteogenic differentiation. Stem cells have self-renewal capacity and differentiation ability into different functional cell types [1]. Thus, biomaterials combined with graphene enable to differentiate of mesenchymal stem cells to osteogenesis. Graphene-based composites help bone repair and differentiation of stem cells with osteogenic potential. Gr and its derivatives can increase the mechanical characteristics and flexibility of materials [100]. The addition of Gr and its derivatives into the scaffold can improve the regeneration of bone osteoconductivity. Besides the improving osteoconductivity, it stimulates both biomineralization and cellular osteogenic differentiation. Graphene oxide provides

an important effect to differentiate different stem cells [103]. As a result of the studies, it has been found that rGO, like GO, provides a great benefit to differentiate stem cells. Especially in 2D cultures, the surface characteristics of the graphene oxide are important for stem cell adhesion and cell proliferation. Both GO and rGO have an enhancing effect on the proliferation and differentiation of stem cells. However, they have some challenges such as cytotoxicity, biodistribution, biotransformation, or immune response, and the challenges should be eliminated [104-106].

**Scaffold**

Bones have an important regenerative property in which they can remodel themselves and repair fractures spontaneously [107]. Bone is capable of regenerating itself when it suffers minor injuries. However, treatment of bone that does not regenerate due to major injuries usually requires surgical application [103]. One of the goals of bone regeneration is to direct root proliferation as well as to allow them to differentiate in a controlled manner with the use of osteogenic inducers and growth factors. After bone damage occurs, mesenchymal stem cells and osteoblasts take part in the healing process [108]. Bone is remodeled by the proliferation and differentiation of osteoblasts and the regenerative properties of osteoclasts [102]. Even if the bones regenerate themselves, this regenerative feature is not enough in severely damaged cases. In such cases, an autologous bone graft can be used for the treatment of the bone. Unfortunately, this method limits the appropriate donor treatment process [109]. Scaffolds have been developed that can enhance bone regeneration to overcome this problem.

The scaffold has an important role in bone regeneration because of its good biocompatibility, biodegradation, supporting cell differentiation, growth and proliferation, and mechanical properties [110]. In addition, the scaffold has a highly porous structure. The highly porous structure allows to adhere of cell and to proliferate it [86].

It can be provided cell spreading and it transports some materials such as nutrients, oxygen, waste, and growth factors thanks to this porous structure. Therefore, it is promoted the sustained development of bone tissue. A scaffold should replace regenerative tissue while retaining the shape and size of the final tissue structure [111].

The design criteria for the fabrication of scaffold are based on biological, mechanical, and physicochemical parameters. Biological factors include the selection of biocompatible and bioactive materials that support the initial adhesion, cellular growth, proliferation, and differentiation. Mechanical parameters ensure the stability of scaffold materials. The outer geometry of the scaffold supplies the micro/macrostructure and interconnectivity of the 3D scaffold. Porosity, pore size, and pore distribution are important criteria for scaffold structure [112]. 3D printing and electrospinning are used in the fabrication of 3D scaffolds. A microenvironment is provided for the adhesion, proliferation, and differentiation of cells by adding therapeutic agents such as proteins, genes, drugs, or bioactive molecules to obtain structure [113]. The scaffold equipped with all these physicochemical stimuli is implanted into the defective bone. After implanting, bone repairing can start (Figure 3). Cell, biopolymer, bioactive molecules, graphene, and its derivatives can be used to gain biological and mechanical properties to the scaffold structure (Figure 4).

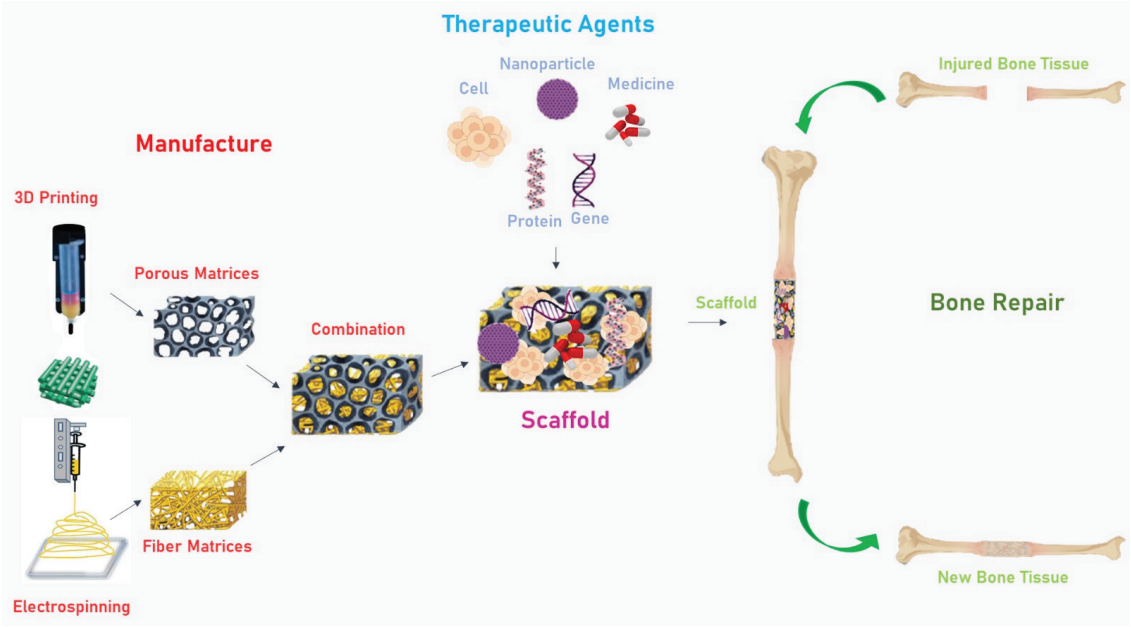


**Figure 3.** Fabrication of scaffold for bone tissue engineering.

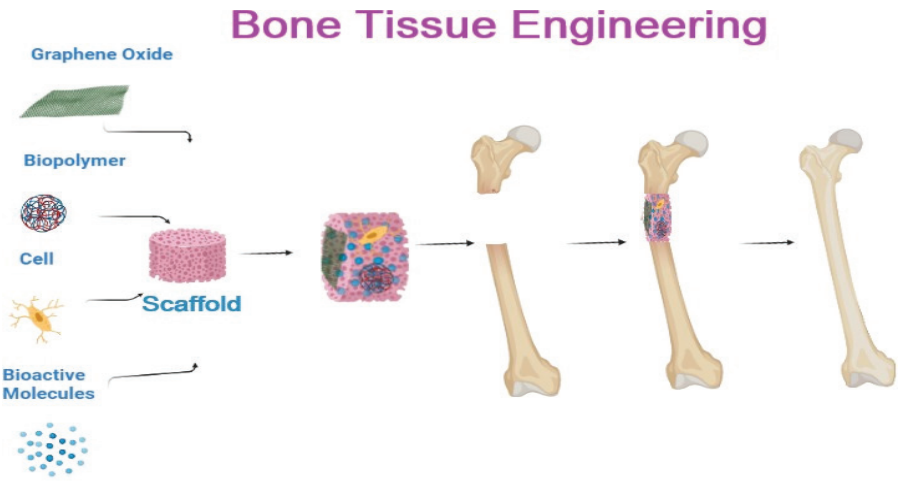


**Figure 4.** Schematic bone tissue engineering process.

Graphene is a suitable material to improve scaffold on bone tissue engineering due to it can enhance the biological characteristics and support the osteoblasts to adhere and proliferate. In the use of biomaterials, it is important to imitate the microenvironment of the extracellular matrix (ECM), which enables cells to attach and proliferate. The mechanical and biological facilities of the microenvironment of the ECM should be considered. However, most of the biomaterials produced are not able to give the mechanical behavior of the extracellular matrix [114]. The mechanical properties of biomaterials are able to adjust according to the mechanical properties of the extracellular matrix with the addition of Gr or GO to biomaterials.

Hydroxyapatite has excellent biocompatibility and osteoconductivity is used in the fabrication of scaffold to regenerate bone. However, hydroxyapatite cannot mediate high proliferation and differentiation rates for osteoblast cells [115]. Moreover, HA cannot provide the required mechanical strength [116]. Therefore, HA and GO are used together in the scaffold to enhance the properties of the osteoconductive scaffold and to expedite the proliferation and differentiation of osteoblasts. The addition of GO to the scaffold for bone regeneration yields very good results [72]. The inducing of cell proliferation, cell viability, migration, and differentiation of the mesenchymal stem cells are affected to bone regeneration. In addition, GO provided the scaffold with the necessary mechanical strength. For example, 3D scaffolds fabricated using hydroxyapatite can be coated with graphene. These scaffolds aid in osteogenic differentiation. So, graphene oxide supports cell adhesion and proliferation [60].

The natural bone mineral nano-HA (nHA) gives good facilities such as osteoconductivity and osteoinductivity. A porous scaffold was fabricated by combining nano-HA with RGO by Nie et al [61]. Positive effects on bone cell growth and mineralization of graphene composite scaffolds were obtained, and an increase in bone repair efficiency was observed in the scaffold. When RGO-nHA scaffold and RGO scaffold were compared, it was obtained that RGO-nHA scaffold had higher cell proliferation, more efficient alkaline phosphatase (ALP) activity, and better osteogenic potential. At the same time, the biocompatibility and ability of bone repair are higher in the RGO-nHA scaffold [58].

Mechanical properties of composites improve with adding of graphene to bioceramics. 45S5 Bioglass® is not able to disturb bioactivity of the scaffolds in the tissue [82]. 45S5 Bioglass®- derived glass-ceramic scaffolds with graphene have many advantages without affecting on the shape and dimensions of porous of scaffold. Result of this, the composite of 45S5 Bioglass® and graphene is able to be used on bone tissue engineering because of its biocompatibility and ability to support cellular activity [117].

Bioglass® with graphene nanoplatelets (BG-GNP) are used in bone tissue engineering applications due to its resulting electrical conductivity. Increasing the graphene nanoplatelets concentration also increases the electrical conductivity of BG-GNP. The bioactivity of BG-GNP is not affected by increasing in electrical conductivity. The fact that the scaffold produced is bioactive and electrically conductive enables it to use in bone tissue engineering applications [118].

In GO-CS scaffolds, it has been observed that cells grow, osteoblastic differentiation, and calcium and phosphate accumulation levels increase at the same time [54]. Saravanan et al. produced scaffolds by freeze-drying by adding gelatin (GN) to graphene oxide and chitosan. It gave positive results in most of the applications in bone tissue engineering with the GO/CS/GN scaffold. It demonstrated remarkable physiochemical properties such as biodegradation, biomineralization, wettability, and protein adsorption.

It also showed the differentiation of mesenchymal stem cells into osteoblasts. The addition of graphene oxide into the scaffold shows that enhancing the swelling property of the scaffold with the hydrophilic functionalities present in GO. The biocompatibility and osteogenic nature of the GO/CS/GN scaffold is proved by the growth of new bone in vivo [40].

Hermenean et al. produced a porous chitosan/GO scaffold. The obtained scaffold showed a remarkable increase in its mechanical properties without losing its flexibility. The flexibility of the produced scaffold was adjustable, and its compressive strength was also increased. Chitosan scaffolds with added graphene oxide significantly increased bone regeneration according to pure chitosan scaffolds [119]. Sivashankari and Prabaharan produced the agarose/chitosan (AG/CS) scaffold. GO was used as a nanofiller in agarose/chitosan (AG/CS) scaffold. Thus, the AG/CS/GO scaffold was produced by the freeze-drying method. This scaffold promoted cell attachment and proliferation [69]. Li et al. used alginate hydrogels as scaffolds in bone engineering. Scaffolds were produced by 3D bioprinting, which allows porous gelatin alginate scaffolds. It was obtained that increment of in adipose-derived stem cell differentiation [107].

Poly (L-lactic-co-glycolic acid) (PLGA) and HA nanofibrous matrices significantly increase the tensile strength. The PLGA/GO/HA matrices provide as mechanically stable scaffolds for cell growth and support functionally alkaline phosphatase activity and mineral deposition. PLGA/GO/HA nanocomposite is preferred in bone tissue engineering applications due to its excellent and versatile scaffold properties [54].

The surface properties of the scaffold are improved with the addition of GO to PLGA/HA scaffolds. The obtaining GO-PLGA/HA scaffold provides to adhere, proliferate and osteogenesis differentiate of cells on the surface of the scaffold. At the same time, loading of GO-BMP-2 onto poly (L-lactic-co-glycolic acid) /hydroxyapatite scaffolds shows good bioactivity, thereby promoting to adhere, proliferate and osteogenic differentiate of cells. Moreover, growth factor consumption was reduced and long-lasting osteoinductive effects were provided by immobilization of BMP-2 via graphene oxide [120]. The use of rGO in scaffolds in bone regeneration, like GO, gave excellent mechanical properties to the scaffold and contributed to the formation of new bone by ensuring to adhere and differentiate of cells [121]. A new scaffold was obtained by adding calcium phosphate cement (CPC) to the GO-Cu nanocomposite scaffold. The resulting scaffold facilitated the adhesion and osteogenic differentiation of cells. It also showed that scaffold (CPC/GO-Cu) significantly increased osteogenesis. The osteogenic differentiation of cells was promoted by increasing the local concentration of drugs or growth factors that are loaded on Gr or its derivatives [122].

Designed microenvironments provide the ability to control and regulate cell-cell and cell-ECM interactions [123]. These microenvironments can regulate the cells to grow up, differentiate, migrate, express of gene, protein synthesise, apoptosis. The understandability of cellular compounds and behaviors is important to create new drug delivery systems and cell-based assays. The resulting cellular microenvironment helps the natural cell functions to be used for regenerative purposes [124].

Simvastatin (SIM) was chosen as the model drug and loaded on porous scaffolds made of silk fibroin (SF) and GO. Cells cultured on SF/GO/SIM scaffold [125] showed a rapid proliferation rate. It is also a scaffold with higher biocompatibility compared to the SF/GO scaffold. Dexamethasone (DEX) is an osteogenic drug that can aid in osseointegration. DEX was first developed on rGO-coated Ti by Jung et al. Thus, it was proved that the drug delivery system can induce the stimulation of osteogenic stem cell differentiation. DEX/rGO-Ti significantly supported the growth and differentiation of cells into osteoblasts. Ren et al. were used DEX together with GO-Ti and rGO-Ti as drugs. Scaffolds of DEX-GO and DEX-rGO helped promote cell proliferation and greatly enhanced osteogenic differentiation. As a result of coating Ti alloys with graphene and its derivatives, controlled drug delivery was achieved [126].

Macromolecular proteins can be loaded into graphene-assembled scaffolds like drugs for bone regeneration. The most ideal osteoinductive protein for bone regeneration is bone morphogenetic proteins (BMP's). The use of GO and hydroxyapatite in the scaffold makes possible the functionality of HA with BMP-2 [127] which is one of the growth factors. The stability of adsorbed proteins such as BMO-2 can be increased by GO. Because of this feature, BMP-2 is loaded on the Ti/GO surface for bone regeneration. Ti/GO/BMP-2 did not lose its 3D conformational stability and bioactivity. In vitro studies have shown that Ti/GO/BMP-2 scaffold increases osteogenic differentiation of human bone marrow mesenchymal stem cells [120].

## CONCLUSION

In this review, the application of biocompatible, mechanically stable Graphene and its derivatives for use in applications of bone tissue engineering is given. Graphene and its derivatives are important materials with remarkable properties to use as scaffolds in tissue engineering. In recent years, research into the development and use of biomedical materials containing Gr and its derivatives has expanded significantly. As a result of the studies, it has been obtained that graphene-based materials have many advantages compared to other materials, such as high surface area, good mechanical strength, good biocompatibility, high biodegradability, gene expression, and proliferation and differentiation in bone cells.

Graphene and its derivatives can be used for bone repairing and regeneration applications as they promote bone cell proliferation and differentiation. The production methods of these materials can enable the use of the materials in many

clinical applications. The value of cytotoxicity that is released from the material is generally admissible in the production of artificial bone tissue. However, some undesirable conditions such as death of cells and limitation of cell growth may also be encountered. Research on the cytotoxicity of graphene is in progress. The control of cell-scaffold interactions of graphene-based materials is easily achieved thanks to the ability of graphene and its derivatives to interact by chemical compositions or functional groups of surface modifications. The presence of oxygen-containing functional groups can enable cell movement and cell-cell communication. Therefore, the spreading of cells on the surface of the scaffold is affected by the chemical composition of the surface and the presence of oxygen-containing functional groups on the surface. The use of graphene and its derivatives in scaffolds helps to improve mechanical strength. The large specific surface area, high mechanical properties, high porosity, and enhanced biological interactions of graphene-based materials enable that these materials can be suitable scaffolds for bone tissue engineering. Consequently, there will be more research-oriented studies of the use of graphene-based materials in bone tissue engineering as it could lead to much more reliable treatments in the near future.

## AUTHORSHIP CONTRIBUTIONS

Authors equally contributed to this work.

## DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

## CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## ETHICS

There are no ethical issues with the publication of this manuscript.

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