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FEATURE ARTICLE

Two-dimensional materials for bone-tissue engineering

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Abstract

There are diverse diseases such as some infections, trauma, and tumor resections during cancer surgery that can cause bone damage or skeletal defects in persons. Most of the time, these defects cannot heal spontaneously due to several medical conditions that patients encounter, like diabetes, hormone-related problems, and autoimmune disorders. This issue is even worse for older people and some special treatments should be provided for them. Bone-tissue engineering has emerged to tackle these challenges. By investigating bone repair strategies, studying bone structures and biomechanics, and employing appropriate growth factors, suitable scaffolds, and biomaterial-centered regenerative approaches can be employed to treat bone defects more effectively. This study reviews some recent bone-tissue-engineering strategies relying on two-dimensional (2D) materials, including graphene and its derivatives, black phosphorus, and MXenes that are exhibiting a great potential in regenerative medicine.

KEYWORDS

2D materials, black phosphorous, bone regeneration strategies, bone-tissue engineering, graphene derivatives, MXenes

1 | INTRODUCTION

Due to situations such as trauma, tumors, and illnesses, bone regeneration in large osseous defects is a key challenge in clinical surgery, and this is still more difficult in case of osteomyelitis and osteitis. Figure 1 illustrates the process involved in bone regeneration.[1] Many treatment techniques have been used, including autografts,

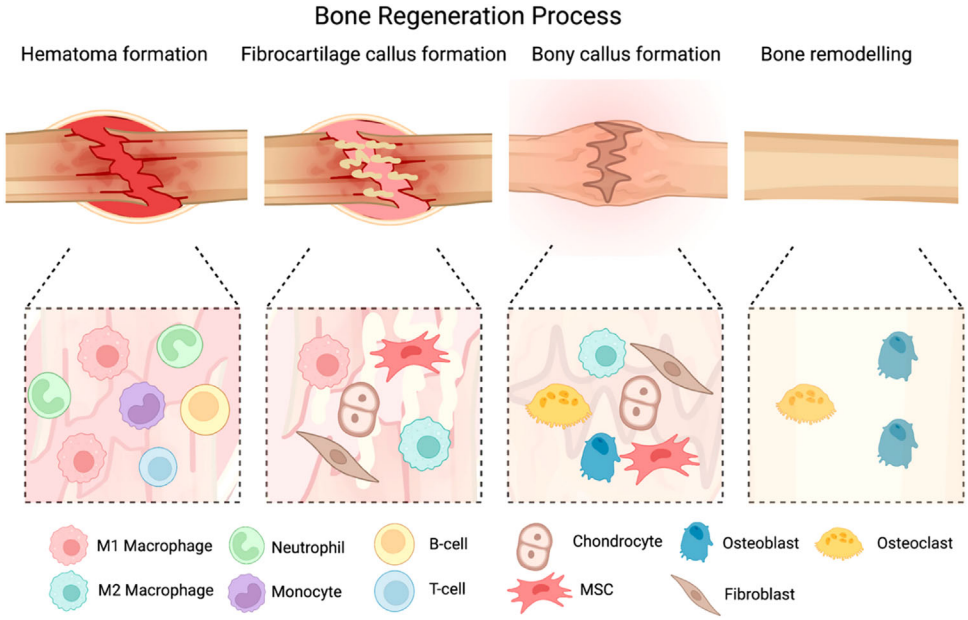

FIGURE 1 Illustration of the process of bone regeneration. MSC, mesenchymal stem cell. *Source*: Reproduced from Ref. [7] under CC license.

allografts, and artificial bone scaffolds. In clinical practice, autografts are the gold standard, but they have several drawbacks, including restricted bone mass, small size range, minimal availability, and donor site injury.

Disease transmission, contamination, and immunological response are all common hazards associated with allografts. As a result, it is critical to produce an artificial bone replacement with superior osteoconduction, osteoinduction, and osteointegration.[2] The utilization of nanomaterial-based composites produced from both natural and synthetic sources has resulted in substantial advancements in bone-tissue engineering for the treatment of a variety of bone abnormalities. Hence, great focus has been placed on the development of artificial bone materials or composites made of polymers, ceramics, and metals, as well as their integration into hard tissue engineering.[3] Furthermore, due to their bone-mimicking characteristics and drug transport behavior, nanomaterials are gaining popularity in bone-tissue-engineering applications, especially related to orthopedics. Although a variety of synthetic and natural biopolymers and bioceramics are now being employed to create artificial bone prosthesis, their usage has often been restricted to laboratory research. Under natural physiological circumstances, creating prostheses with distinct, bone-mimicking qualities is difficult. Furthermore, employing nanotechnology, nanomaterials, scaffolds, and cell-based biomaterials, numerous researchers have sought to make artificial bone. For one or more uses, most nanomaterials have been proven to be appealing for biomedical applications and to carry important added values. Many have a high capacity for bone-tissue building, have superior mechanical qualities, are noncytotoxic to osteoblasts, and have inherent antibacterial capabilities (without the use of any exogenous antibiotics). Nanobiomaterials have been studied extensively for bone-tissue-engineering applications, either as a matrix material or as an extra-reinforcing phase in a variety of polymeric nanocomposites, due to their beneficial qualities. Diamond, fullerene, graphite, carbon nanotubes (CNTs), and graphene are some of the allotropes of carbon that are accessible in isoforms. CNTs and graphene, among these nanocarbon materials, show promise in biomedical applications, such as nanoelectronic biosensing, drug transport, and bone-tissue engineering.[4,5] Since their discovery in 1991, 24 types of CNTs, which are one-dimensional (1D) macromolecules, have been exploited in a variety of biological applications owing to their exceptional mechanical, electrical, and physical characteristics.[6]

Single-walled carbon nanotubes (SWNTs) and multi-walled carbon nanotubes (MWNTs) have been the most widely investigated biomaterials among the several forms of CNTs. SWNTs and MWNTs were used to study comparative mesothelial invasion. In comparison to MWNTs with a comparable aspect ratio, SWNTs have a higher affinity for binding to the cell membrane. Apart from CNTs, other interesting classes of two-dimensional (2D) nanomaterials with potential biomedical applications include black phosphorus (BP) nanosheets, also known as phosphorene, and MXenes, which are covered in this review. Promises in the context of bone scaffold development are particularly highlighted.

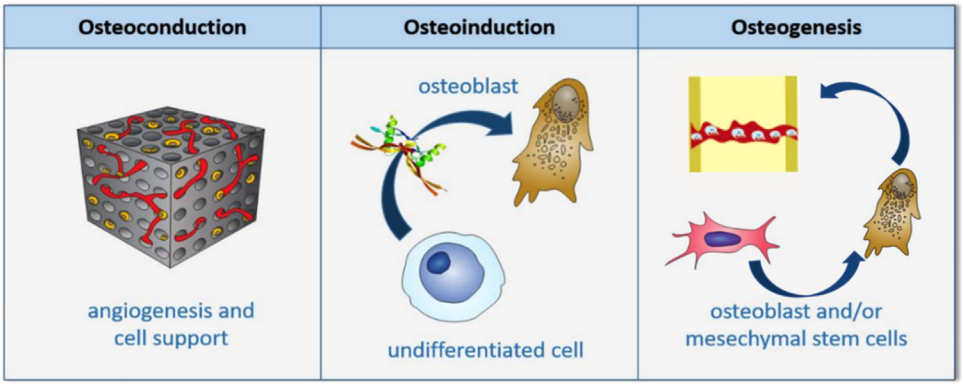

FIGURE 2 Diagram showing mechanisms of osteoconduction, osteoinduction, and osteogenesis. *Source*: Reproduced with some modifications from Ref. [22] under CC license.

2 | BONE REGENERATION STRATEGIES

Bone is an essential organ in human bodies because not only provides structural support, load-bearing for moving, and physical protection of the interior organs but also serves as a foundation for hematopoiesis and tissue regeneration because the bone marrow contains a large number of hematopoietic stem cells and bone marrow-derived mesenchymal stem cells (BMSCs) that can differentiate into different types of blood cells and osteocytes.[7,8,9]

Bone is made up of living bone cells organized in a biomineral media based on calcium phosphate (CaP).[10] Bone is made up of a variety of cell types, such as osteocytes, osteoblasts, and osteoclasts that are all entrenched in an intricate microenvironment.[11] Osteoblasts and osteocytes are engaged in bone synthesis, whereas osteoclasts are involved in the resorption and remodeling of existing bone tissue.[12] It is helpful to grasp two principles of bone regeneration for tissue-engineering structures, that is, osteoconduction (angiogenesis and cell support) and osteoinduction (stimulation of undifferentiated cell differentiation), before examining the required properties of prospective tissue-engineering materials, as seen in Figure 2. The capacity to allow pluripotent cells from a nonosseous environment to differentiate into chondrocytes and osteoblasts, ending in bone formation, is known as osteoinduction. Osteoconduction promotes the formation of bone by allowing capillaries and cells from the host to develop into a three-dimensional (3D) structure.[13] An osteoinductive substance permits repair in a place that would typically not recover. On the other hand, an osteoconductive substance guides restoration in a region where normal healing will occur.[14] The biomineral medium of bone is made up of approximately 30% organic and 70% inorganic parts.[15] Type I collagen accounts for 90% of the organic segment, with non-collagenous proteins, lipids, proteoglycan molecules, osteopontin (OPN), and other bone matrix proteins forming the remaining 10%. The mechanical strength and tissue adhesion properties of bone matrix proteins are critical.[16] Calcium (Ca^{2+}) and phosphate (PO_4^{3-}) ions efficiently stimulate cell proliferation and differentiation.[17] Clinically, the healing of bone abnormalities induced by trauma or certain disorders such as tumors is still a difficult task.[18] Although bone tissue generally has some self-healing potential, this ability is hindered when the bone defect surpasses a critical value (2 cm) or when the defect is caused by orthopedic illnesses like tumors or infections.[19] If bone healing fails, ischemia, osteonecrosis, and bone loss will occur, resulting in nonunion of the bone.[20] Bone graft transplantation by using autologous or allogeneic bone is a common treatment although carrying some limitations associated to the donation site and risk of disease transmission, respectively.[21,22]

Specifically, donor site problems, restricted tissue availability, immunological rejection, and other issues must be addressed when using these procedures.[23] Additional therapies to encourage bone regeneration are necessary to prevent these issues. On the other hand, artificial bone replacements with exceptional osteoconduction, osteoinduction, and osteointegration have had a lot of success in recent decades.[24]

To build biomimetic scaffold platforms for bone regeneration, a variety of methodologies have been used. Just to mention an example involving 2D carbon nanomaterials, a silk fibroin/hydroxyapatite (HA) scaffold can be loaded with micro-RNAs using graphene oxide (GO). This scaffold can promote osteogenic differentiation and mineralized bone production in defects without loading osteoblast cells.[25] Despite significant progress, designing various scaffolds with porous structures and the right constituents, loaded biomolecules, acceptable mechanical characteristics, and high bioresorbable properties remains a difficult task. Overall, utilizing 2D bioceramics meet the

bone regeneration criteria, which represents the key goal in view of clinical usages.

3 | BONE STRUCTURES, BIOMECHANICS, BIOLOGY, AND GROWTH FACTORS

Bone is the most important component of the human skeletal system, since it provides structural function, supports mechanical movement, protects organs, and produces and hosts blood cells. The cortical bone and trabecular bone are the two layers that makeup bone. Except for 3%–5% of space for canaliculi and osteocytes, cortical bone is compact and thick.[26] Cortical bone is made up of many tiny columns of bone matrix, each of which is called osteon. Multiple layers of osteoblasts and osteocytes surround a central canal known as the Haversian canal in each column. The basic multicellular units (BMUs) continually reconstruct mineralized bone in the columns, coordinating the actions of osteoclasts and osteoblasts and responding to mechanical loading according to Wolff's rule.[27] Trabecular bone is made up of a rodlike matrix that provides space for the movement of cells, marrow, and blood vessels. It is a porous network with a larger bone surface-to-bone volume (BS/BV) proportion than compact bone. Unlike cortical bone, where BMUs must originate from an existing Haversian or Volkmann's canal, BMUs in cancellous bone originate from the exterior of the trabeculae.[28]

The quality of bone tissue is determined by both bone biomechanics and total bone structure. Biomechanical test findings can be evaluated for clinical significance by looking for correlations with characteristics often utilized in clinical practice, such as bone mineral density (BMD) and bone geometry.[29]

Natural bone has a wide range of mechanical characteristics depending on age and body area. Natural bone has anisotropic Young's modulus and yield stress. The compact bone is stronger and more rigid in its longitudinal direction than in its transverse direction. The porosity and organization of the particular trabeculae dictate the mechanical characteristics of the trabecular bone, which has a porous structure.[26]

When external loading surpasses the load-bearing capability of the bone, it fractures. This, however, might happen due to a variety of reasons. The bone matrix may be weak due to poor physico-mechanical qualities such as low ultimate strength, or the shape of the bone may be affected due to a thin cortex or low BMD. Mechanical tests are typically done on bone specimens of a specified (standard) geometry, the preparation of which is frequently tricky when it comes to bone. To begin with, the bone specimen must be molded or trimmed to a predetermined form that is suitable to the mechanical test. Furthermore, if the bone is porous, the test must account for the porous geometry, which is especially critical in trabecular bone.[30]

The tissue features inside the calcified matrix, also known as bulk tissue properties, determine the properties of the bone matrix. They are influenced by collagen fiber organization, mineralization of the bone matrix, organic matrix composition, and interactions between mineral and organic phases. The micro-architecture (porosity or trabecular architecture) or the macro-architecture (gross geometry) of bone determines its geometrical qualities (overall shape and cortical thickness). Pore percent, trabecular quantity and density, the interconnectivity of trabecular bone, trabecular direction (anisotropy), bone mass, cortical breadth and thickness, and ultimately the overall form of the whole bone may all be used to examine these geometrical features.[31]

Bone is a unique substance in the sense that it may be described as flexible and weak in terms of strength and hardness. Its flexibility is due to the collagenous matrix, which affords the bone exceptional tensile load support. Within lamellae, collagen fibrils are piled in a parallel order to produce a fibril array, and there are four different fibril array patterns.[32]

Furthermore, bone is a delicate material, and the mineral elements that determine its capacity to withstand compressive stresses have a substantial impact on its fragility grade. The orientations of force application will vary the bone behavior due to these biomechanical features of bone. Diverse forces, including compression, tension, shear, bending, and torsion, may be applied to bones depending on the directions of loads.[33] In general, bone tissues of long bone may be able to withstand larger stresses in the longitudinal direction and less orthogonally to the major axis, which makes sense given that bone absorbs the majority of its loads in this direction.[34]

Natural bone is made up of cells, an ECM made up of collagen fibrils, HA, and associated minerals. Under dry circumstances, collagen and HA combined make for 95% of natural bone.[35] Biological apatites include ion substitution elements, such as Na^+, Mg^{2+}, Cl^-, K^+, F^-, and Zn^{2+}, which differ from the stoichiometric composition of HA.[36]

Bone cells, which include osteoblasts, osteoclasts, bone lining cells, and osteocytes, are important for bone growth, shape, and maintenance. The osteoblast is in charge of bone creation, whereas the osteoclast is in charge of bone remodeling by resorbing damaged and defective bones. The modeling and remodeling procedures help to keep the created bone in place and aid in fracture healing growth factors (GFs) are proteins that govern a variety of cellular activities (such as survival, proliferation, migration, and differentiation), and they play an important role in BTE.[37]

Bone morphogenetic proteins (BMPs) are one of the most researched GFs, having been identified by Urist in 1965. They are a family of cytokines that relate to the transforming GF family. BMPs have been frequently employed in BTE to improve bone regeneration by encouraging bone marrow progenitor cells to become bone cells, due to their important functions in bone formation. The binding of BMPs to serine–threonine kinase receptors on the cell surface triggers particular intracellular pathways that stimulate gene transcription, influencing cell proliferation and differentiation.[38]

4 | POPULAR 2D MATERIALS FOR BONE-TISSUE ENGINEERING

Nanomaterials are materials with one or more of their three dimensions defined on a nanoscale varying from 1 to 100 nm or even more. Typically, the thickness varies between a few angstroms to a few nanometers.[39] 2D nanomaterials are extremely thin nanomaterials with high degrees of anisotropy and/or practicality.[40] The sideward dimension-to-thickness ratio of 2D materials is tremendously high.[41] 2D materials have outstanding physicochemical features that facilitate their uses and make them a much more appealing topic for researchers. Biocompatibility and biodegradability have been demonstrated in some of these 2D materials, which are very desirable for biological and medical purposes. So far, investigators have discovered a wide range of 2D materials that have numerous applications in biomedicine, as shown in Figure 3.

Tissue-engineering technology has brought emerging research paths and concepts for the treatment of bone abnormalities in the past few years, owing to the continuing invention and development of biomaterials. This technology integrates engineering and cell biology principles and technologies to create biomaterials that can repair and rebuild the function and structure of injured tissues.[42–44] After being damaged, bone tissue has the inherent potential to self-repair. This potential, meanwhile, can be deficient in complicated clinical situations when considerable quantities of newly formed bone are required or the regenerating process is hampered.[45] Also, with rising in the prevalence of bone disorders and ailments throughout societies, it is more important than ever to find approaches to overcome present restrictions and produce bone graft replacements that could regenerate bone in whole capacities. There are some characteristics and aspects of an ideal bone graft, as described below.

For cell and tissue ingrowth, an ideal synthetic bone graft must be porous with adequate interconnected pore dimensions, mechanically capable of matching the characteristics of the host bone and bearing as well as conveying loads, stimulate the viability of progenitor cells and their differentiation into bone cells that result in the induce osteogenesis and osteoinduction, be osteoconductive, causing bone cells to proliferate, grow, and adhere to its surface, be biocompatible and maintain normal cellular function in the host tissue without causing local or systemic toxicity. Furthermore, after a while it is expected to biodegrade under controlled conditions that harmonize with the formation of new bone.[46,47,48]

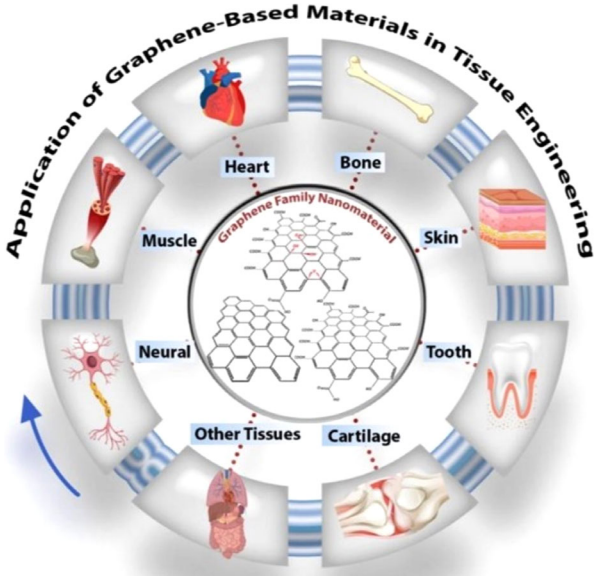

FIGURE 3 Schematic of two-dimensional (2D) nanomaterials and their application in biomedicine. *Source*: Reproduced from Ref. [48] under CC license.

Recognizing the structure and function of native bone tissue, as well as the proper choice of biomaterials, is needed for desirable materials design for bone-tissue engineering.[49] The material that constructs the scaffold and determines its functionality indeed plays an essential role in bone-tissue engineering. The discovery of novel materials with appealing attributes such as high biocompatible, undisturbed secure biodegradation, the capabilities to facilitate cell differentiation, growth, and differentiation, and the acceptable ability to withstand the stress of physical forces, is necessary for tissue regeneration effectiveness.[60] As summarized in Table 1, we review the extensive application of 2D materials in various bone-tissue engineering and then describe their forthcoming uses in bone therapy based on their properties.

4.1 | Graphene and its derivatives

One of the main vital elements in all human and animal organs is carbon. It has mostly provided humans in the

TABLE 1 Two-dimensional (2D) materials used for bone tissue and tissue engineering.

Type of 2D material	Modifications/composites	Form of application	Study type	Results	References
BPNS	Bioactive glass	Support or a scaffold	In vivo	NIR photothermal conversion Promoted osteogenesis	50
BPNS	Hydrogel	Support or a scaffold	In vivo and in vitro	Increased biocompatibility Performance in the NIR region	51
Nb_2C MXene	*S*-Nitrosothiol (R-SNO)-grafted mesoporous silica, bioactive glass	Support or a scaffold	In vivo	Improved osteosarcoma ablation Enhanced bone regeneration	52
Nb_2C MXene	(R837)-loaded mesoporous silica, bioactive glass	Support or a scaffold	In vivo	Increased inhibition of metastasis of breast cancer to the bones Enhanced bone imperfection reparation	53
rGO	Hydrogel	Support or a scaffold	In vivo and in vitro	Increased immune expression Decreased inflammatory response	54
GO	Poly(2-hydroxyethyl methacrylate) and gelatin	Support or a scaffold	In vitro	Efficient differentiation into osteoblasts	55
GO	Chitosan and glycerophosphate hydrogels	Support or a scaffold	In vitro	Promoted osteogenic differentiation	56
GO	Alginate–chitosan–collagen	Support or a scaffold	In vitro	Substantial increase in cells attached	57
Nano-hydroxyapatite-GO hybrid nanofillers	Silk fibroin hydrogel	Support or a scaffold	In vitro	Promoted in vitro osteogenic differentiation	58
Graphene	Polyacrylamide hydrogels	Support or a scaffold		Significant improvement in biocompatibility	59

Abbreviations: BPNS, black phosphorus nanosheets; GO, graphene oxide; NIR, near-infrared; rGO, reduced graphene oxide.

form of food and energy for centuries. In the last century, in addition to its prevalent uses, it has received much attention from researchers in the nanomaterials area.[37,61] Hitherto, around 500 theoretical 3-periodic allotropes of carbon are known,[62] including graphene. Since its discovery in 2004, graphene has attracted a growing amount of attention due to its extraordinary features, including high electron mobility, great loading capacity, high elastic modulus, and excellent biocompatibility.[63–67] Graphene would be seen as a single atomic sheet that is approximately transparent, which is comprised of a one-atom-thick 2D sheet of sp^2 hybridized carbon atoms that have been arranged according to a hexagonal symmetry.[68,69]

Graphene is a flexible material with a large specific surface area of nearly 2600 $m^2\ g^{-1}$ for a single graphene sheet.[70] Each carbon atom includes the three in-plane σ-bonds, which contribute to graphene's perfect planarity, and one out-of-plane π-bond that can interact with other atoms.[71] This one-of-a-kind structure has given graphene exceptional mechanical, electrical, thermal, and chemical stabilities as well as optical attributes, which outperform those of any other material, with some even beyond theoretically expected limits.[72] Besides, graphene shows intrinsic strength of 130 GPa, electrical mobility of $2 \times 10^5\ cm^2\ V^{-1}\ s^{-1}$, great light pellucidity of 97.7%, and Young's modulus of 1 TPa.[73–76] Graphene has an exceptionally high thermal conductivity at ambient temperature, for a suspended single-layer graphene was found to have a thermal conductivity value of 5000 $W\ m^{-1}\ K^{-1}$.[77] Nevertheless, the hydrophobic nature of graphene may affect the interaction of membrane-associated proteins, resulting in cellular toxicity.[78] Moreover, pristine graphene in hydrophilic types of media and physiological fluids has weak dispersibility.[72]Graphene functionalization, on the other hand, has been considered to be an effective approach to minimize its toxicity and increase its dispersibility, especially for its usage in the medical field.[79]

Two of the most important graphene derivatives are GO and reduced graphene oxide (rGO), as shown in Figure 4. Graphene may indeed be oxidized, and exfoliation of graphite into a single layer is performed to produce amphipathic GO, which can then be subsequently reduced to generate rGO.[80] One specific advantage that GO has over rGO and pristine graphene is that it is always more attainable to accomplish functionalization. Having various functional groups, such as epoxy, hydroxyl, and carboxyl groups, makes it much easier to bind to a variety of biomolecules and, accordingly, expands the biological applications of GO.[79] Graphene and its derivatives (GDs) can potentially be used in a variety of areas, including biotechnology, polymer science, electronics, photonics, optics, catalysis, energy storage, and biomedicine.[79,81] In the medical area, graphene and particularly its derivatives might be used as drug delivery carriers,[82] phototherapeutic agents in curing cancer,[83,84] substances in tissue engineering[85,86] that serve as an anchor for cell proliferation and differentiation, biosensing, bioimaging, and so forth.

4.2 | Black phosphorus (BP)

Since BP nanosheets were first delaminated from bulk BP in 2014,[87] researchers have been fascinated by BP nanomaterials, also known as phosphorene, which is a family member of 2D substances. Apart from BP nanosheets (BPNSs), BP nanoparticles, and BP quantum dots have also attracted great interest in many high-tech and biomedical fields.[79] In single-layer BP, the phosphorus atom and three adjacent atoms are covalently connected in sp^3 hybridized orbitals, and weak Van der Waals forces preserve the interaction amongst layers.[88] As a result, exfoliating layers of BP from the bulk crystal become facile. To construct BPs with varying numbers of layers and dimensions for biomedical applications, typically liquid exfoliation procedures[89] are implemented. BP nanomaterials expose in-plane anisotropy that emanated from a unique puckered orthorhombic structure.[87,90,91,92] Furthermore, BP has excellent properties that are useful in bone-tissue regeneration as shown in Figure 5 and summarized in Table 2. This structural anisotropy gives BP many distinct characteristics, including optical and electronic features with a large tunable energy bandgap (0.3–2.0 eV),[93-95] and thermal, mechanical, and geometric properties.[96,97] Moreover, due to the biocompatibility and biodegradability of this material, BP demonstrates to be suitable in contact with the physiological environment.[98] Phosphate ions or phosphonates are the biodegradation products of BP; they are naturally found in bone tissue and are involved in the mineralization of bone.[99] For instance, Wang et al. reported that hydrogels containing BP can induce mineralization, boost osteogenic cell differentiation, and promote bone rebuilding.[100] As a bone ingredient, phosphorus accounts for almost 1% of the entire body weight.[101] Phosphate ions not only are found in the blood and have no health risks and toxic effects but are also essential to skeleton growth and bone repair, facilitating osteogenesis and osteointegration.[50,102] Because of these characteristics, BP is a highly desired 2D material for phototherapy of cancers,[103] bioimaging,[104] biosensors,[105] theranostics,[106] drug delivery,[107-109] scaffolds for implantation into the body,[110] and other bioengineering and biomedical applications. Even so, the use of this biodegradable material for tissue engineering is now in its early stages, with relatively, limited investigations provided.[50]

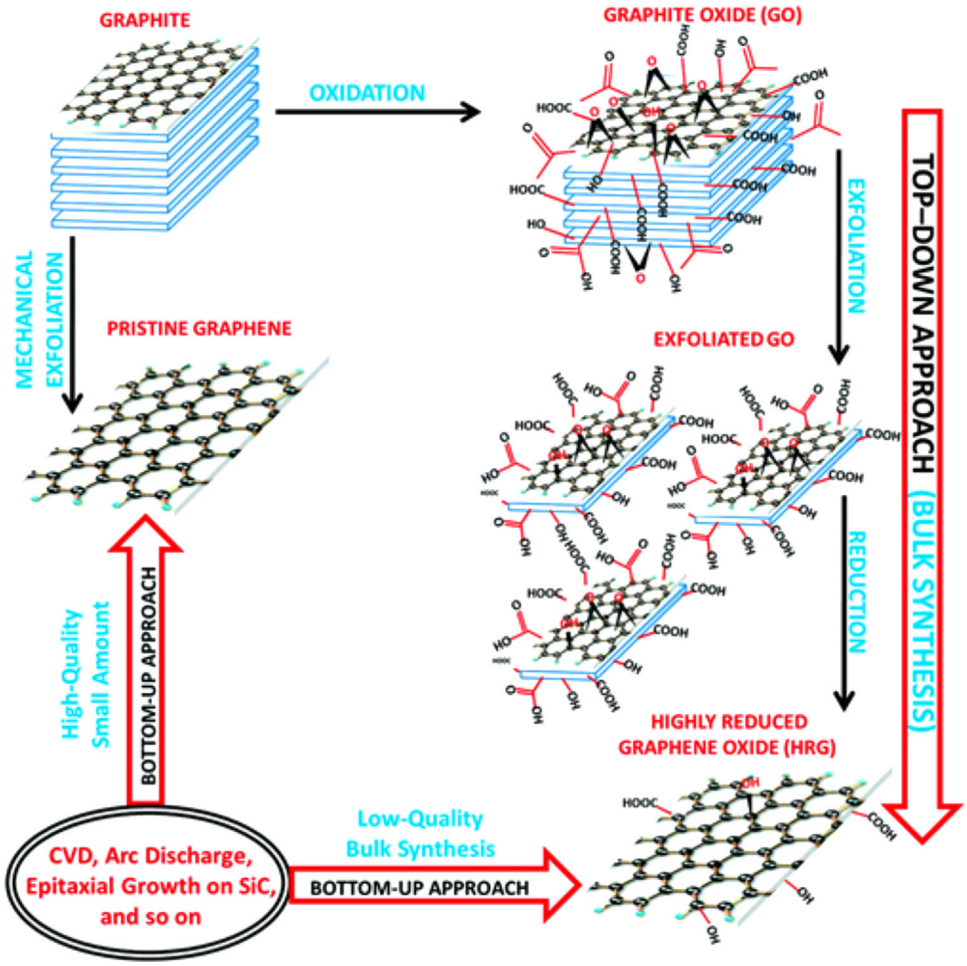

FIGURE 4 Illustration of the different approaches in the synthesis of graphene derivatives, graphene oxide (GO), and reduced graphene oxide (rGO). *Source*: Reproduced from Ref. [86] under CC license.

TABLE 2 Black phosphorous (BP) nanomaterials in bone tissue engineering.

Type of BP material	Type of study	Outcomes reported	References
BP nanosheets-enabled DNA hydrogel	In vivo and in vitro	Promoted blood vessel growth and induced osteogenesis	111
BP-enhanced injectable hyaluronic acid	In vivo and in vitro	Reestablished infected wound	112
BP nanosheets incorporated fish-gelatin hydrogel	In vitro	Promoted osteogenesis	113
BP hybrid	–	Increased osteogenic gene expressions	114
BP/collagen/poly(ε-caprolactone) nanofiber matrix	In vitro	Improved osteogenic differentiation	115
BP/β-tricalcium phosphate/doxorubicin/peptide scaffold	In vivo	Reduced the long-term toxicity	116
BP quantum-dots functionalized aptamer	In vivo	Promoted biomineralization	117
BP nanosheets poly(lactic-*co*-glycolic acid)	In vivo and in vitro	Increased osteogenesis promotion	99

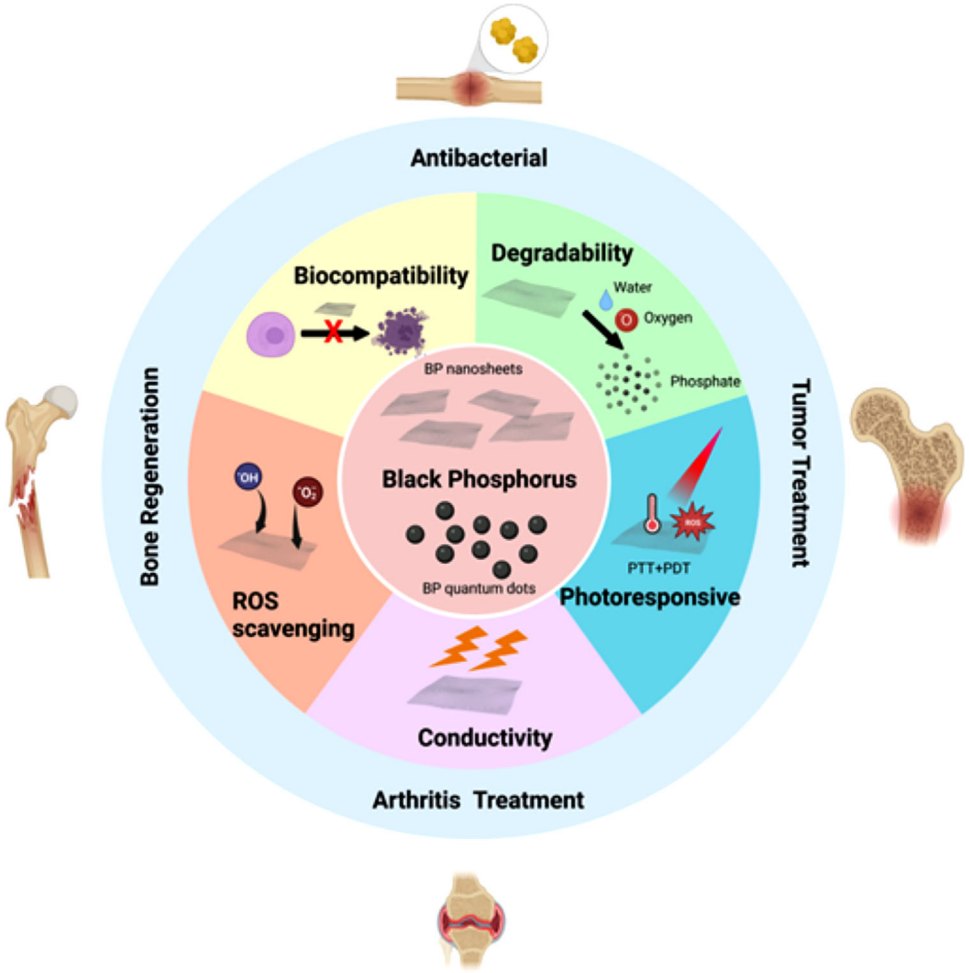

FIGURE 5 Properties of black phosphorus (BP) and its current application in bone tissue engineering. ROS, reactive oxygen species. *Source*: Reproduced from Ref. [92] under CC license.

4.3 | MXenes

In 2011, scientists at Drexel University discovered MXene, a novel 2D material that is made up of transition metal carbides, nitrides, and carbonitrides.[118] In the appellation of MXene, "MX" indicates that it derives from MAX phase ceramic materials, and "ene" originated from graphene, because of its 2D sheetlike structure.[119,120] MAX phase ceramic materials are trinary and/or multi-carbide, nitride, or carbonitride substances in which the "M" stands for primary transition metal elements (Cr, V, Sc, Mo, Ta, Nb, Zr, Ti, Hf, etc.), the letter "A" represents an IIIA or IVA element from the periodic table (i.e., groups 13 or 14) like Si or Al, and "X" denotes carbon or nitrogen.[121,122] MXene has the chemical formula $M_{n+1}X_nT_x$, where "M" and "X" possess a similar definition as within the MAX phase, and *n* illustrates the stoichiometric number, which can be 1, 2, 3, or maybe 5 (in MAX phase),[123] and "T" describes the surface-terminated functional groups, such as hydroxyl (−OH), fluorine (−F), and oxygen (= O) on MXene sheets.[124] Whenever "A" is eliminated from the MAX phase, "T" is required to poise the broken charge neutrality in MXene. It should be noted the exact value of x is undetermined.[119] There are over 70 different MAX phases discovered by now,[122] and also the fact that non-MAX phases may be involved to generate MXene[125] enhances the designability and variety of MXene in abundant ways. According to this wide range of MAX phases, at least 30 different MXenes have been identified to date, including $Ti_3C_2T_x$, $Nb_4C_3T_x$, V_2CT_x, and multiple more.[126] MXene has a crystalline nature that is quite close to MAX phase ceramics. Diverse MAX phases could have resulted in a broad assortment of MXenes with dissimilar features.[121] Furthermore, adding functional groups impacts the properties of MXenes, thereby augmenting the MXene diversification more than before.

Excellent chemical and physical attributes of MXenes have attracted much attention from researchers in recent years. The MXene sheet has remarkable mechanical capabilities, including tremendous flexibility and strength, due

to the MX bond being one of the strongest recognized chemical bonds.[123] MXenes can outspread in physiological environments due to their hydrophilic inherent.[126] Furthermore, since Ti, Ta, and Nb are rather inactive in physiological environments, some MXenes are biocompatible with biological organisms with insignificant toxicity, and a recent research has shown the biodegradation of MXenes in rats.[127] MXenes also have a high light absorption in the near-infrared (NIR) biological window, rendering them superior in phototherapy and photoacoustic imaging.[128] MXenes hold acceptable chemical stability,[129] large specific surface areas,[130] excellent electrical conductivity, and high hydrophilicity.[131] These appealing properties make MXenes desirable options in energy storage,[132] environmental engineering,[133] catalysis,[134] and finally biomedical applications,[135] including tissue engineering,[136] drug delivery,[137] antibacterial activity,[136] photothermal therapy (PTT),[138] cancers treatment,[139] biosensing,[140] and so on.

5 | THE APPLICATIONS OF 2D MATERIALS FOR BONE REGENERATION

Bone-tissue engineering is a strategy for improving bone regeneration at bone defects by integrating biomaterials, cells, and osteogenic agents. Due to the superior physical and chemical attributes of 2D materials, such as biodegradability and biocompatibility, as well as excellent mechanical capabilities and load-bearing, and so on, the use of 2D materials in BTE has risen in popularity in recent years. In the following, the application of these sheet-like materials is specifically discussed in the context of bone-tissue engineering. Available research on relatively recent BP and MXene has been thoroughly reviewed; as regards the graphene family and the relevant derivatives that have already received much attention, the most important and significant investigations from 2018 onward have been considered.

5.1 | The applications of graphene and its derivatives for bone regeneration

Because of remarkable electron transport, physicochemical, and mechanical characteristics, as well as its large specific surface area, GDs have become a focus of extensive scientific attention. This emerging 2D nanomaterial family can increase osteoclast cellular activities in vitro, such as growth, adhesion, proliferation, mineralization, and osteogenic differentiation, as well as enhance bone regeneration in vivo.[141]

Some in vitro studies have demonstrated that integrating a modest quantity of GDs into substances such as scaffolds or nanocomposites can positively improve osteoblast activities like proliferation and adhesion. The potentials of GD-based materials to improve cell adhesion, viability, and proliferation are due in part to their high ability to adsorb proteins. Adsorbed proteins form a coating that facilitates cell attachment, spreading, and growth. The π-electron cloud in graphene interacts with the internal hydrophobic region of proteins to aid protein binding, whereas the oxygen functional groups in GO enhance adsorption by electrostatic interaction.

Scaffolds are crucial in bone-tissue-engineering research because they act as frameworks for new bone-tissue development and formation and supply structural backing to certain cells. Scaffolds promote regenerating bone and can also be utilized to infuse bioactive agents that speed up tissue recovery and formation time. Biocompatibility, osteoinduction, osseointegration, and osteoconductive properties should be included in scaffolds for bone regeneration.[60]

GDs can be embedded in scaffolds as a valuable component for bone regeneration usage. In 2018, Liang et al. used the freeze-drying method to construct three-dimensional spongy nano-HA/poly(lactic-co-glycolic acid)/GO (nHAC/PLGA/GO) scaffolds, which they subsequently cocultured with MC3T3-E1 cells, as shown in Figure 6. The findings of that study indicated that the nHAC/PLGA/GO (1.5 wt%) scaffold enhanced osteoblast (MC3T3-E1) adherence and growth as compared to GO-free nHAC/PLGA scaffold at days 3, 5, and 7. Specifically, the cells were relatively vaster and much more stretched on the GO-containing scaffold.[142]

Furthermore, since GDs endow stem cells with a special physical structure similar to the natural ECM, they may indeed be capable to adjust the osteogenic differentiation of stem cells from various sources. For instance, Newby et al. synthesized GO nanoscale particles with a 6%–10% oxygen content, then cocultured them with human mesenchymal stem cells (HMSCs), and used alizarin red staining and quantitative analysis to assess the influence of graphene nanoparticles on osteogenic differentiation of HMSCs. According to their observations, the amount of calcium of HMSCs cocultured with GO nanoparticles stood considerably higher than that of cells on the control surface. Intriguingly, the significant increase of cellular activity was found in the lack of any osteoinductive substances (e.g., bone morphogenetic proteins), suggesting that GO nanoparticles might inherently cause calcium aggregation in HMSCs on their own.[143] For a more detailed example, Krukiewicz et al. manufactured integrated GO/poly(methyl methacrylate) (PMMA) composites. The osteogenic differentiation efficacy of human mesenchymal stem and progenitor cells cultured on GO/PMMA composite was then investigated

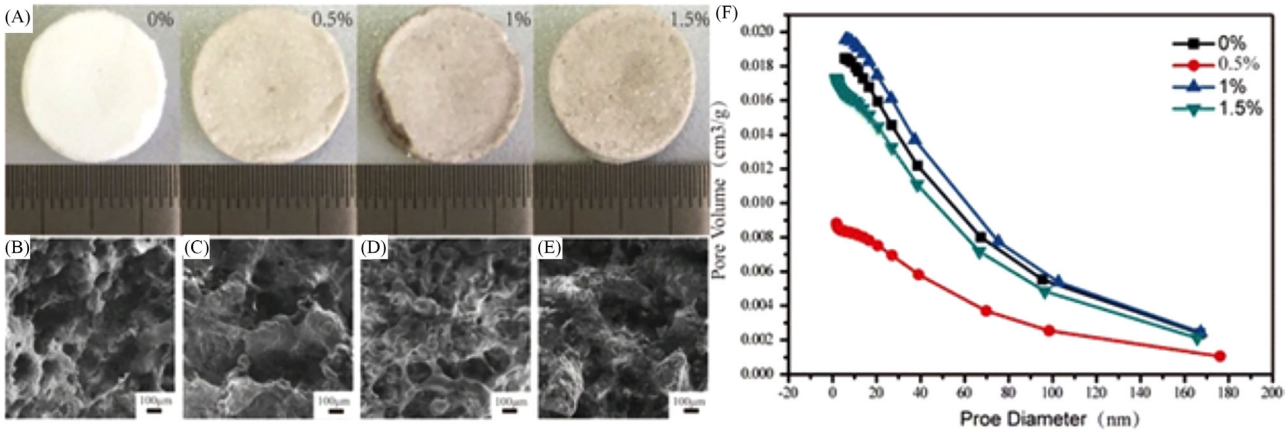

FIGURE 6 (A) Optical image of the fabricated nano-hydroxyapatite/poly(lactic-*co*-glycolic acid)/graphene oxide (nHAC/PLGA/GO) scaffolds with a diverse amount of GO. (b–e) SEM pictures of (B) nHAC/PLGA, (C) nHAC/PLGA/GO (0.5 wt%), (D) nHAC/PLGA/GO (1.0 wt%), and (E) nHAC/PLGA/GO (1.5 wt%) scaffolds. (F) Hole distribution of nHAC/PLGA/GO (0, 0.5, 1.0, and 1.5 wt%). *Source*: Reproduced from Ref. [142] under CC license.

using three differentiation markers: alkaline phosphatase (ALP), secreted protein acidic and rich in cysteine, and bone morphogenetic protein-2 (BMP-2), with the outcomes revealing that GO/PMMA composites have been effective in stimulating osteogenic differentiation and were more promising compared to pure PMMA.[144]

GDs can be incorporated into other materials, such as metals, natural polymers, and mineral phases for achieving enhanced efficiency and synergistic purposes. In 2019, Lyu et al. applied anodizing and SF/GO self-assembly to develop multilayer ZnO nanotubes/silk fibroin/GO nanomaterials (SF/GO-ZnO) on raw zinc surfaces. They also loaded the osteogenic drug dexamethasone (Dex) on the surface of the composite to additionally enhance the efficiency of the structure. The study indicated that SF/GO-Dex-ZnO exhibited outstanding antibacterial and osteogenic potential, which could be ascribed to GO's special structure and the active oxygen generated from ZnO decomposition. The sharpness and stiffness of the GO 2D nanomaterial damaged the cell membrane of bacteria via straight physical contact. Furthermore, the cells on the composite with SF/GO coating self-extended in various orientations, but the cells on raw zinc and anodized zinc were lengthened, demonstrating that the SF/GO covering had a great impact on cell proliferation and division. The aforementioned findings might be explained by the fact that the composition of SF is nearly identical to collagen, the primary element of the ECM, and GO seems to have a better adsorption performance for serum protein, leading to a larger density of adhesion molecules that can be employed for improving cell proliferation and adhesion. As a result, SF and GO functioned together as complementary substances to enhance cellular growth and proliferation.[145] Because inorganic compounds like HA make up a substantial part of bone composition, the ability to accelerate the biomineralization of inorganic materials in natural bone was seen as a key indicator in bone regeneration.[146] Zhao et al. developed GO/chitosan/nano-HA particles (GO/CS/nHAP) scaffolds via incorporating nHAP into a framework including covalently bonded CS and GO. The result demonstrated that the scaffolds exhibited exceptional physiochemical features, such as three-dimensional spongy bone structure, mechanical characteristics, and biodegradation. Moreover, in vitro investigations showed that, in comparison to the defect in the CS/nHAP sample, the defect in the GO/CS/nHAP group was approximately completely covered with regenerated bone tissue and created a coherent framework with natural bone.

Polymers have long been employed as bone regeneration components due to their many benefits, including processability into three-dimensional with high porosity frameworks, degradability, and mechanical attributes that are similar to the implanted tissue. Several polymers, including polycaprolactone (PCL) and poly(lactic acid) (PLA), are hydrophobic with no functional groups, which can be led to an undesirable biological propensity. One of the remarkable features of GDs is their capability of uniformly distributing or spreading in almost all polymeric matrices.[147] Recently, Unagolla et al. used 3D printing to construct PCL–GO composite scaffolds that could regulate the dimensions and pore radius of the implants separately. The morphological analysis revealed that the area of the pure PCL scaffold was hard and uneven, whereas the surface of the GO-based nanostructures was smooth and even. Besides, the addition of GO particles increased the nanocomposite fluidity. The compositional analysis detected the presence of calcium and phosphorus, thus indicating that GO increased scaffold mineralization when

compared to GO-free PCL-based scaffolds. Western blot examination revealed that the high porosity of GO and PCL nanocomposite scaffolds boosted the release of BMP-2 and OPN, confirming that this integrated structure encouraged osteogenesis.[148]

Collagen is a natural biopolymer that is commonly employed in biomedicine. Collagen-based scaffolds stand not harmful to living tissue, are capable of being decomposed, and are bioactive with minimal immunogenicity. Nonetheless, poor mechanical strength makes collagen scaffolds unsuitable for most of bone-regenerative applications. In 2018, Zhou et al. added GO to collagen in order to increase the biomineralization potential of the final composite. The collagen–GO constructs were immersed in simulated body fluid for 1 week, yielding the uniform formation of bone-like apatite with a Ca/P proportion close to that of natural bone. After 12 weeks, this resulted in much more bone-tissue growth in mice cranial lesions, accompanied by a doubling in bone volume and density.[149]

Dental scaffolds containing GDs impact the osteogenic and odontoblastic development of dental pulp stem cells and periodontal ligament stem cells, allowing them to be employed in dental tissue regeneration. For example, the ability of GO to promote alveolar bone regeneration and periodontal attachment rehabilitation was proven by implanting GO-coated collagen sponges in periodontal class II furcation defects in beagle dogs.[150] Similarly, Wu et al. recently prepared PLGA/graphene nanoplate films that caused higher alveolar bone healing in Sprague-Dawley rats after 2 months,[151] emphasizing the significant potential of GDs Family nanocomposites in dental usage.

When GO is added to hydrogels, the physical, biological, and chemical attributes of polymers improve as well. The addition of GO to chitosan/glycerophosphate thermoresponsive hydrogels facilitated protein adsorption, swelling propensity, biomineralization ability, and the potential to induce osteogenic differentiation in MSCs.[56,152] The incorporation of GO to injectable thermosensitive hydrogels of poly(polyethylene glycol citrate-*co*-*N*-isopropyl acrylamide) and gelatin (PPCNg) kept the hydrogels thermoresponsive and boosted ALP activity and osteogenic gene expression in mesenchymal progenitor immortalized mouse adipose-derived cells (iMADs). These composite hydrogels were subcutaneously injected into BMP9-transduced iMADs in athymic nude mice, giving rise to mineralized, greatly vascularized trabecular bone that was substantially more grown and denser compared to the PPCNg hydrogels.[153]

The great attributes of this substance do not end there. Other appealing properties of GO include its strong NIR light absorbance and high photothermal conversion efficiency. In this regard, Ma et al.[154] fabricated a novel temperature-sensitive multifunctional composite scaffold comprising nano-sized HA, GO, and chitosan, which can simultaneously kill osteosarcoma cells while promoting osteogenesis at the defect site. Specifically, cancer cells could be killed due to GO-associated photothermal effect under 808-nm NIR irradiation by reaching a temperature of 48°C and bone regeneration was stimulated by the presence of HA. Furthermore, this scaffold exhibited a good hemostatic effect, thus facilitating the overall healing of osseous injury.

Research has also revealed that 2D materials may easily access friction surfaces because of their highly narrow sheet formations and low shear strength between each layer, avoiding the friction surfaces from straightforwardly contacting each other, and reducing the friction coefficient.[155] For instance, a CuO/rGO nanocomposite was synthesized by Meng et al. and its lubricating effect was examined. The results demonstrated that 0.06 wt% CuO/rGO inclusion dramatically decreased the friction factor (−46.62%) and wear rate (−77.05%).[156] Concerning the thin film deposition feature of 2D materials, researchers believe that incorporating these materials into the area of contact of artificial joints might be an applicable approach to enhance the operational life of artificial joints by improving lubrication and lowering friction.

According to previous research, however, GDs can cause cytotoxicity by exhausting mitochondrial membrane potential and raising intracellular reactive oxygen species (ROS), which can lead to apoptosis. Additionally, the dimensions, form, concentration, and degree of functionalization of GDs were all linked to possible cytotoxicity. These concerns about GDs potential cytotoxicity and possible residues in vivo are the most significant challenges for bone healing material and manifestly for other biomedical applications.[157–160]

5.2 | The applications of BP for bone regeneration

Biocompatibility, biodegradability, PTT, photodynamic therapy (PDT), and high drug-loading efficiency are only a few of the remarkable features of BP nanomaterials that show great promise for biomedical purposes, especially bone-tissue engineering. About 85% of the total phosphorus of the human body belongs to bones and teeth.[161] It is reported that BP can be oxidized and degraded in vivo, producing nontoxic PO_4^{3-} ions.[99,110] This can provide essential phosphorous for bone-tissue regeneration. The phosphate ion can make CaP deposits when combined with Ca^{2+}, which promote biomineralization and speed up bone healing.[162] Thus, it is plausible trying to incorporate BP into bone-tissue engineering to treat bone defect.[79] In a recent research, Huang et al.[163] developed a BP-based

scaffold by employing a novel technique that catches calcium ions via phosphorus supplied by BP photoresponsive deterioration, thus boosting mineralization and bone-tissue regeneration. In addition, an in vivo test in rabbits showed that these scaffolds highly promoted bone formation at the injury site.

BP has also been combined with other 2D materials to produce composites for bone-tissue-engineering applications. To induce bone regeneration, Liu et al. developed a composite of GO and BP to be applied on 3D-printed poly(propylene fumarate) scaffolds. The designed GO nanosheets improved cell adhesion, protein adsorption, provided large surface area, and surrounded BP to ensure constant PO_4^{3-} release, which drives cell osteogenesis and new bone development. In consequence, the cell shape became extended, and cellular filaments grew along the margins. These findings showed that integrating 2D BP with GO stimulated cell division and bone formation synergistically, thereby suggesting this technique to be a reliable path for bone-tissue regeneration.[91] Biologically active ions like strontium (Sr^{2+}) and magnesium (Mg^{2+}) are highly studied because of their ability to facilitate osteoblast differentiation and osteogenesis, thus being of high significance in the context of bone-tissue engineering. Wang and colleagues integrated BP and $SrCl_2$ into PLGA microscopic hollow spheres, and NIR irradiation was used to elicit local Sr^{2+} release. They found that the synergistic impact of Sr^{2+} and PO_4^{3-} could lead to more considerable bone regeneration ability.[102]

One of the outstanding properties of BP 2D material is its great photothermal conversion efficiency. Tong et al. synthesized BP/PLGA osteoimplant to evaluate osteogenetic effect under NIR light irradiation. This osteoimplant contained only 0.2 wt% BP. The results showed that NIR-exposed osteoimplant increased the local temperature to 40–42°C, therefore increasing the level of heat shock proteins besides accelerating bone healing.[99]

As mentioned before, one of the considerable features of BP nanomaterials is the ability to elicit PTT and PDT effects. The BP nanomaterials could be employed to promote bone regeneration even in the case of tumor and bone infection. For instance, Yang et al. incorporated BPNSs into a 3D-printed bioactive glass (BG) scaffold, resulting in a dual-functional BP–BG scaffold that protects against osteosarcoma while also promoting osteogenesis. During a 2-week observation period, they reported that tumors on rats of the BP–BG scaffold group were destroyed by irradiation using NIR light, accompanied by no recurrence. Besides, the micro-CT data demonstrated that BP–BG scaffolds could repair bone deficiency better than pristine BG scaffolds.[50] Similarly, Raucci et al. reported BPNSs to have differential effect on healthy or tumor cells. These 2D materials decreased and limited the metabolic activity of osteosarcoma cells, but concurrently increased the cell growth and osteogenic differentiation of human preosteoblast cells.[164]

Orthopedic implants are employed for rigid tissue applications to take place of bones and joints, rectify malformations and abnormal forms, restore fractions, and so on. Every orthopedic implant carries the risk of infection, which can lead to implant failure and rejection in the long term. Since drug resistance to conventional antibiotics is an increasing issue at the moment, it is challenging to find new methods to improve the antibacterial properties of orthopedic implants.[79] 2D materials offer interesting physicochemical characteristics due to their distinct structures, and so bear a broad variety of functions, such as antimicrobial behavior. The antibiotic-similar effect was seen by Xiong et al. in BP 2D nanomaterials against both gram-positive and gram-negative bacteria. They confirmed bacterial toxicity in a time- and concentration-dependent manner and observed that the maximal bactericidal efficacy of BP 2D nanomaterial against *Escherichia coli* and *Bacillus subtilis* was 91.65% and 99.69%, respectively, after 12 h exposure.[165] Another amazing feature of BP is the capability to successfully treat infections caused by bacteria without creating antibiotic resistance via generating an abundance of ROS.[166] Earlier investigations indicated that BP-based integrated materials maintain—or even potentiate—those promising bactericidal properties which are typical of the pure BP nanomaterials.[167] Aksoy et al. created a nanocomposite by integrating gold (Au) nanoparticles into BPNSs to improve BP antimicrobial properties. When irradiated in the NIR region, the fabricated nanocomposites of BP/Au could generate more heat and also had more effective antibacterial features than pure BP.[168,169] To summarize, BP 2D materials could be an excellent option for achieving antibacterial effects with improved efficiency in biomedical applications, especially in bone-tissue engineering.

The chemotactic factors deployment of osteoblast precursor cells to damaged locales, as well as the enhanced differentiation of osteoblast precursor cells and the mineralization of ECM, are two critical stages in promoting bone-tissue regeneration. In 2020, Cheng et al. employed the micro-sol electrospinning technique for fabricating poly(lactic acid) (PLA) electrospun fibers coated with BMP2-loaded BPNSs. They found that the loaded BMPs were released through the composite and utilized to stimulate osteoblast precursor cell differentiation. Moreover, phosphate ions from BP degradation enclosed Ca^{2+} for performing a mineralization function and precipitate in situ. In vitro and in vivo tests confirmed the outstanding bone regeneration performance of these novel BP-PLA nanofibrous scaffolds containing BMP2.[170]

TABLE 3 Some applications of MXene nanomaterials in bone tissue engineering.

Type of MXene	Composite or modification	Type of study	Outcomes reported	References
Ti_3C_2	MXene/RSF hydrogel	In vitro	Promoting direct osteogenesis	177
Ti_3C_2	GelMA/β-TCP/sodium alginate (Sr^{2+})/MXene	In vivo	Accelerates the healing of infection and bone regeneration	178
Ti_3C_2	–	In vivo and in vitro	Excellent biocompatibility	179
Ti_2AlN	(Ti_2AlN)/polycaprolactone	In vivo and in vitro	Improved in situ bone repair	180
$Ti_3C_2T_x$	MXene NPs-integrated with PLCL and collagen	In vivo	Promoted spontaneous osteodifferentiation	181
Ti_3C_2	MXene/UHAPNWs	In vivo	Enabled bone regeneration	182
Ti_3C_2	MXene quantum dots	In vitro	Aids in tissue repair and treatment of inflammatory	183
Ti_3C_2	CaO_2–TiO*x*@Ti_3C_2, C-T@Ti_3C_2	In vivo and in vitro	Promoted osteogenic transformation and enhanced bone quality	184

Abbreviations: PLCL, poly(L-lactide-*co*-*ε*-caprolactone); UHAPNWs, ultralong hydroxyapatite nanowires.

5.3 | The applications of MXenes for bone regeneration

MXenes are one of the emerging kinds of 2D nanomaterials that are becoming employed in various biomedical applications, as summarized in Table 3. This is due to their excellent biological compatibility, high specific surface area, and great physical and chemical characteristics. MXene nanostructures were shown to be highly cytocompatible and promoted osteogenic differentiation in vitro, according to the report of recent research. MXene nanostructures also demonstrated high biocompatibility, osteoinductivity, and bone regeneration function in vivo when placed into subcutaneous regions. To improve the mechanical and biological possessions of MXene, Fu et al. added ultralong hydroxyapatite nanowires (UHAPNW) as a reinforcing phase. In this investigation, to establish stronger interactions between 1D UHAPNWs and 2D MXene nanosheets via hydrogen bonds, multiple nanosheets were employed to integrate with ultralong nanowires. The inclusion of UHAPNWs facilitated cell adhesion, proliferation, and osteogenic differentiation while also improving mechanical characteristics and hydrophilicity. As a result, bone repair in a rat calvarial bone defect was expedited. Moreover, the authors showed that the incorporation of 10 wt% UHAPNWs into MXene yielded the highest Young's modulus and tensile strength.[171]

In 2017, Lin et al. showed that MXenes are particularly suitable in the potential therapy of osteosarcoma. The authors reported that, after intravenous administration, Nb_2C nanosheets behaved as a photothermal transformation nanoscale agent for NIR-caused photonic hyperthermia against breast cancer.[172] More recently, the same investigators employed ultrathin Nb_2C MXene nanosheets that were merged into a 3D-printed bone-mimetic BG scaffold (BGS), called NBGS, for providing the composite scaffolds with the distinctive ability of photonic bone malignancy ablation in the NIR-II biological window, while stimulating osseous restoration through ameliorated neovascularization (Figure 7). First, they utilized photothermal hyperthermia to attack bone-tumor cells after implanting multipurpose NBGS. After then, considerable vascularization appeared to stimulate new osseous formation, followed by slow degradation of the scaffolds; overall, the associated formation of blood vessels and bone structures was favorable for the efficient repair of massive bone defects. Eventually, the study indicated that 2D Nb_2C MXene incorporated with BGS had the potential to promote angiogenesis, which is key to allow osseous regeneration in large bone defects.[173]

MXene-based materials have been used successfully in guided bone regeneration (GBR). The premise behind GBR therapy, which is extensively used for orthodontic implantation, oral rehabilitation, and periodontal regeneration, is to use a membrane to protect the bone from soft tissue interference.[40] The application potential of multilayered $Ti_3C_2T_x$ MXene films in GBR has been studied by Zhang et al., who found that $Ti_3C_2T_x$ MXene films are extremely cytocompatible and appropriate for cell spreading and proliferation in vitro due to MMXene's rough shape and hydrophilicity. The functional groups of $Ti_3C_2T_x$ provided negative charges to the surface of MXene films, resulting in an electrically charged microenvironment appropriate for bone defect regeneration.[174]

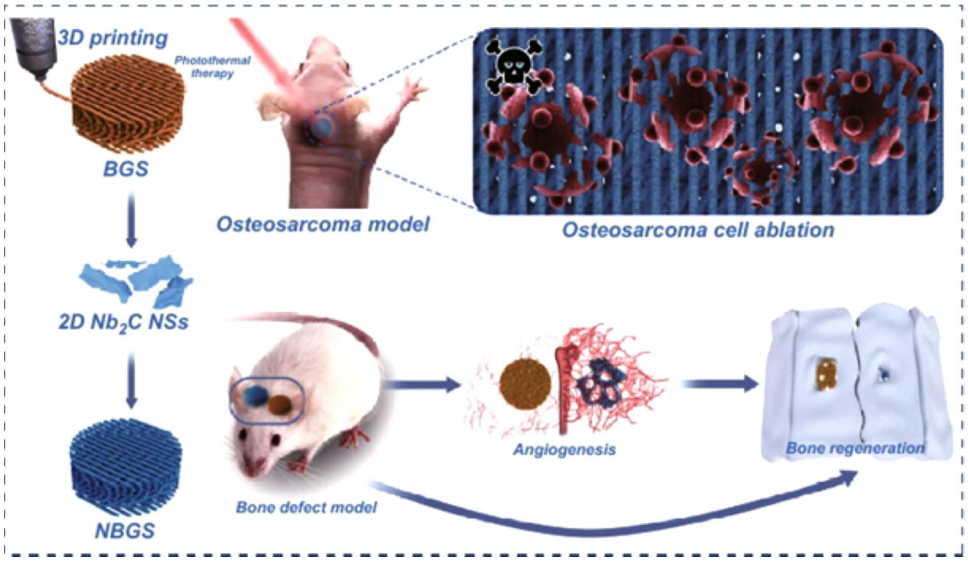

FIGURE 7 The process for photothermal ablation of osteosarcoma and bone regeneration. *Source*: Reproduced from Ref. [173] under CC license.

Furthermore, $Ti_3C_2T_x$'s hydroxy groups could establish hydrogen bonds with proteins, hence impacting on cell differentiation. According to in vivo testing, MXene films offered a high bone regeneration capability because they lead to rapid mineralization and early osteogenesis. However, when employed as a barrier membrane in GBR, MXene films have some disadvantages and restrictions.[175] In another study, Chen et al. developed $Ti_3C_2T_z$/PLA nanocomposite membranes for GBR purposes. Using *N*-octyltriethoxysilane as a connection between hydrophilic $Ti_3C_2T_z$ nanosheets and hydrophobic PLA increased ultimate tensile strength considerably. The results showed great biocompatibility, including improved cell adhesion, proliferation, and osteogenic differentiation.[176]

Recently, Awasthi et al. used the electrospinning method to produce MXene/PCL fibers that were more cytocompatible with pre-osteoblast cells as compared to fibroblast cells. They reported that MXene increased the wettability of the composite fiber matrix, facilitating cell attachment and proliferation. They also illustrated the bioactivity of these materials in terms of phosphorus/calcium accumulation and in vitro biomineralization, which led to adequate osteointegration. Eventually, they concluded that these composite fibers could be used for bone regeneration and wound dressing applications, although more investigations are still necessary.[185]

In recent years, for simultaneously executing photonic bone-tumor destruction and bone-tissue regeneration, Pan et al. combined 2D Ti_3C_2 MXene with 3D-printed BG to obtain composite scaffolds. They observed that these Ti_3C_2-BG (TBGS) materials gave a perfect growing environment and space for human bone marrow mesenchymal stem cells (hBMSCs), attracting them to attach to the scaffold surface. According to this research, TBGS was claimed as biocompatible and could increase cell proliferation. It is also worth mentioning that TBGS could be employed as a biomaterial to induce the osteogenic differentiation of hBMSCs in vitro. Finally, in vitro and in vivo comprehensive tests proved that these Ti_3C_2MXene-integrated composite scaffolds effectively promoted the death of bone cancer cells. Concurrently, the incorporation of 2D Ti_3C_2 MXene into the composite BG scaffolds has shown to significantly promote the formation of new bone tissue. In summary, these Ti_3C_2 MXene-integrated composite scaffolds showed promise as potential candidates for the treatment of bone tumors owing to their dual therapeutic action for cancer cell apoptosis and bone-tissue engineering.[128]

6 | CONCLUSIONS AND FUTURE PERSPECTIVES

To repair diseased tissue and related function at the bone injury site, 2D biomaterials have been designed to promote endogenous regrowth ability in circumstances when healing and restoration are impeded.[186] Due to their extraordinary characteristics, 2D materials may be able to perform in several ways, independently or combined together in order to ensure a synergetic effect to accomplish the best therapeutic outcome; the latter approach indeed expands further the utilization of 2D materials in biomedical research. As mentioned previously, the use of 2D materials in clinical trials still faces some challenges.

The process of photothermal conversion is a case in point. 2D nanomaterials are used to damage inflammatory tissue by providing elevated temperatures and ROS. It is a fact that high temperatures can damage inflammatory tissue, but there is a significant risk that normal tissues like the meniscus and cartilage will be harmed, too. On the other hand, controlled PTT would allow the selective killing of cancer cells while leaving healthy cells almost undisturbed. In this regard, the development of multifunctional scaffolds, encompassing both 2D nanomaterials able to kill cancer cells upon NIR irradiation and bioactive substances to stimulate bone-tissue regeneration, is a great promise for improving the clinical treatment of tissue injuries like osseous defects from osteosarcoma resections. However, PTT has obvious restrictions in penetration depth that have to be taken into account.

Several scientists have looked into using GDs to create bone biomaterials with improved physicochemical and mechanical characteristics. The good mechanical features of GDs, as well as their attractive physicochemical properties, can be employed to reinforce scaffolds and implants and create biomaterials that can endure the load-bearing conditions of bones. The graphene family of materials is increasingly gaining attention for bone-tissue-engineering applications, particularly for its possible uses in avoiding bacterial resistance and stimulating stem cell osteogenic differentiation. The biocompatibility of GDs is critical before they are evaluated for clinical trials in biomedical applications. However, some obstacles must be overcome. GDs also have a lot of potential in the GBR and controlled drug delivery. The mechanical characteristics of biodegradable membranes consisting of collagen or chitosan are improved by graphene family compounds without affecting their unique properties. By using π–π stacking, electrostatic forces, and hydrogen chemical bonds, osteogenic drugs or osteogenic proteins can be adsorbed on graphene or its derivatives with great efficiency. Considering all of the benefits, graphene family materials have a lot of prospects for bone-tissue regeneration.

As regards the application of BP for BTE, the full potential of this class of nanomaterials has not been fully exploited yet. In the context of bone regeneration, BP is predominantly used in the form of nanocomposites. The BP-based nanomaterials demonstrate the potential for osteosarcoma disease therapy and bone healing strategies like the NIR-triggered drug delivery systems. In addition, previous research has shown that integrating 2D BP with GO can increase cell proliferation and osteogenesis in a complementary manner. Many 2D composite materials offer features that BP alone cannot, including great stability; therefore, introducing various 2D materials composites to the domain of bone regeneration could bring novel ideas and impressive outcomes. As a result, the combined nanomaterials approach offers a feasible path for BTE applications. Many obstacles remain in the application of BP nanostructures in BTE, from primary studies to clinical usage. As mentioned, BP is regarded to have high biocompatibility since it is unstable under physiological environments and easily dissolves into phosphate ions, which are nontoxic to cells. On the other hand, Shao et al. recently discovered that 2D BP may identify and connect to Polo Like Kinase 1 (PLK1) in the centrosome, which is essential for cell cycle progression. PLK1 activity would be decreased after binding with 2D BP, and the cell cycle would be stopped in the M phase, eventually resulting in cell apoptosis.[187] To prevent BP from deteriorating, it has been suggested to encapsulate with PLGA or polydopamine. This finding acts as a warning to take precautions while using 2D BP in BTE applications. To get the strongest positive impacts from the treatment, future research should investigate techniques to maximize the balance between stability and biodegradability.

Being an increasingly applied 2D material for bone formation and GBR therapeutics, MXene is extremely biocompatible, with significant osteoinductivity. Proliferation, viability, adhesion of cells, and osteogenic differentiation were all improved using MXene nanosheets. According to current research, MXene-integrated composite scaffolds successfully promoted the death of bone cancer cells and accelerated the formation of new bone inside and in contact with composite BG scaffolds. These MXene-integrated composite scaffolds are quite advantageous for bone cancer therapy due to their simultaneous capability of inducing bone-tumor death and healthy bone repair. Furthermore, some MXene nanomaterials are prospective multifunctional bioscaffolds with great promise in bone regeneration and photonic-responsive medical approaches in the treatment of osteosarcoma. The existing shortcomings of these nanostructures include mass production, in vivo retention, formation accuracy, preservation, and long-term biosafety, which all obstruct their broad use in bone regeneration and must be overcome in the next future. To sum up, due to their special structure, possible osteogenic functionality, and intrinsic biocompatibility, MXene and MXene-based nanostructured materials will have the potential to make a significant contribution to BTE.

As noted previously, bone tissue, as well as its different structural arrangements, is complicated. Although significant progress in bone formation has been made to this point, more research is necessary to understand what is required to arise a marketable tissue-generated bone. The strategy of mixing and exploiting the benefits of multiple 2D materials to generate composites with a synergetic impact could be a route to get the strongest therapeu-

tic efficacy and expand the use of 2D nanostructured materials in bone therapy.

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