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Chapter

Graphene-Based Nanosystems: Versatile Nanotools for Theranostics and Bioremediation

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Abstract

Since its revolutionary discovery in 2004, graphene— a two-dimensional (2D) nanomaterial consisting of single-layer carbon atoms packed in a honeycomb lattice — was thoroughly discussed for a broad variety of applications including quantum physics, nanoelectronics, energy efficiency, and catalysis. Graphene and graphenebased nanomaterials (GBNs) have also captivated the interest of researchers for innovative biomedical applications since the first publication on the use of graphene as a nanocarrier for the delivery of anticancer drugs in 2008. Today, GBNs have evolved into hybrid combinations of graphene and other elements (e.g., drugs or other bioactive compounds, polymers, lipids, and nanoparticles). In the context of developing theranostic (therapeutic + diagnostic) tools, which combine multiple therapies with imaging strategies to track the distribution of therapeutic agents in the body, the multipurpose character of the GBNs hybrid systems has been further explored. Because each therapy and imaging strategy has inherent advantages and disadvantages, a mixture of complementary strategies is interesting as it will result in a synergistic theranostic effect. The flexibility of GBNs cannot be limited to their biomedical applications and, these nanosystems emerge as a viable choice for an indirect effect on health by their future use as environmental cleaners. Indeed, GBNs can be used in bioremediation approaches alone or combined with other techniques such as phytoremediation. In summary, without ignoring the difficulties that GBNs still present before being deemed translatable to clinical and environmental applications, the purpose of this chapter is to provide an overview of the remarkable potential of GBNs on health by presenting examples of their versatility as nanotools for theranostics and bioremediation.

Keywords: Graphene-based nanomaterials, graphene, graphene oxide, reduced graphene oxide, graphene quantum dots, cancer theranostics, green synthesis, bioremediation

1. Introduction

Since its first serendipitous but groundbreaking discovery by Geim and Novoselov in 2004 [1], followed by the 2010 Nobel Prize in Physics, graphene has drawn tremendous interest from scientists from every direction to exploit many of its special features. Indeed, graphene and graphene-based nanomaterials (GBNs) have distinctive mechanical, electronic, optical, and chemical properties [2–4]. Graphene and GBNs can therefore be found in numerous applications in the areas of electronics, physics, and material science [5–7]. In recent times, considering an emerging opinion on the eco-friendly characteristics of graphene and its derivatives, researchers have agreed to use these nanomaterials in other fields of science, for example in medical [8–13] and environmental applications in bioremediation [14–21].

One of the most interesting applications of GBNs in the medicine field is its use as theranostic tools, i.e. taking advantage of its properties to provide a combination strategy for both therapy and diagnosis [8]. Multiple combinations of different therapeutic and diagnostic strategies are currently being used to achieve a therapeutic effect with GBNs. Since each strategy has inherent advantages and limitations, a combination of complementary strategies can result in a synergistic theranostic effect [8]. Of all diseases, the synergistic theranostic effects of GBNs can be more significant in cancer. In fact, despite all the resources expended in clinical advances, cancer remains the world's leading cause of death, with a confirmed mortality rate of 8.8 million by 2015. In addition, the World Health Organization (WHO) and International Agency for Research on Cancer (IARC) expect all cases of cancer to rise to 21.2 million by 2030 [22, 23]. With conventional approaches to cancer treatment, such as chemotherapy and radiation, tumor-initiating cells also designated as cancer stem cells (CSCs), are hard to eradicate [24]. The survival of residual CSCs is therefore believed to drive the onset of tumor recurrence, distant metastasis, and drug resistance, which is a major clinical problem for effective cancer treatment [24]. Therefore, new cancer therapy approaches such as GBNs are urgently necessary to address this clinical need [8, 24].

Another field that requires investment in research is the use of GBNs in bioremediation. Air, water, and soil pollution is a worldwide challenge for the environment and human society [17, 18, 25]. The removal from the environment of multiple pollutants, including inorganic and organic compounds, is a growing concern [17, 18, 25]. The most harmful and hazardous pollutants that have been the focus of the GBNs' bioremediation research will be discussed in this chapter and listed according to the following classes: volatile organic compounds, inorganic metals, organic dyes, polycyclic aromatic hydrocarbons, pharmaceuticals, pesticides. In water sources and the atmosphere, these chemical pollutants also have the property of degrading and producing carcinogenic and mutagenic compounds [20]. In addition, microbial drug resistance can also be caused by bioaccumulation of contaminants such as pharmaceutical drugs, pesticides and their by-products in water bodies [20]. Therefore, pollution damages ecosystems but also affects human health, and the large number of pollutants emitted annually by industries and households have had a major impact on the environment and human existence.

This chapter presents an overview of the properties of graphene and GBNs and their synthesis by classical and green methods. In addition, the use of GBNs will be described either in medicine (as theranostic tools) or in bioremediation (as adsorbents and photocatalysts) and these different aspects will be presented as part of their versatile beneficial use when applied to human health.

2. Graphene and GBNs

Graphene is a single layer of sp² hybridized carbon atoms bound together in a planar 2D honeycomb structure.

GBNs are graphene-like structures that can be obtained from graphene or graphite as the starting material, but that possess sp² and sp³ hybridized carbon atoms and differ from one another in terms of surface chemistry, number of defects and lateral dimensions (**Table 1**). GBNs include graphene derivatives, such as graphene oxide (GO), reduced graphene oxide (rGO), graphene quantum dots (GQDs). GO is a highly oxidized form of graphene that contains oxygen functional groups (e.g., epoxide –O–; carboxyl –COOH; hydroxyl –OH) either in the plane or at the edges. rGO is a reduced form of GO where most of its functional oxygen groups have been removed. As a result of oxygen removal processes, rGO has more in-plane defects than GO and graphene. On the other hand, due to oxidation processes, GO has more defects than pristine graphene. GQDs consist of one or more layers (up to ten layers) of graphene or rGOs with a lateral size below 30 nm.

3. Properties of graphene and GBNs

Many fascinating properties of graphene, including strong thermal and electrical conductivity, large surface area and excellent mechanical properties, have been discovered since 2004 (**Table 1**). Further data on the properties of graphene can be found elsewhere [37, 38]. Herein, we focused on the properties of graphene and GBNs that are most significant for their biomedical and environmental applications and emphasized how these exceptional properties are connected to the special 2D carbon atomic honeycomb structure of graphene and its derivatives.

3.1 Mechanical properties

Because of the 2D carbon atomic honeycomb arrangement, each carbon atom is covalently bound to three neighbouring atoms inside a graphene layer. The tight C-C covalent bonds are responsible for graphene's extraordinary structural rigidity and a single defect-free graphene sheet is thus approximately 200 times mechanically stronger than steel. This explains the outstanding mechanical parameters of graphene: Young's modulus of 1 TPa, Poisson's ratio of 0.149 GPa and fracture strength of 130 GPa [27] (**Table 1**).

The mechanical properties of GO and rGO are significantly affected compared to graphene and depend on the surface groups and defects left over from oxidation or other treatment processes. However, the rigidity of these GBNs is still particularly high. Graphene's extraordinary structural rigidity and the still excellent mechanical properties of GBNs mean that these nanomaterials can potentially be used in medical devices, hydrogels, biodegradable films, electrospun fibres and other tissue engineering scaffolds to fill or strengthen the structures of these materials [39].

3.2 Thermal and electrical properties

Graphene is a monoatomic layer of sp² hybridized carbon atoms arranged as a honeycomb lattice. The π - π bonds below and above the carbon atomic plane impart exceptional thermal and electrical conductivity to graphene. In fact, a carbon atom normally has four electrons for bonding, but in graphene every atom allocates a single unbound electron that walks freely through the crystal lattice and leads to excellent electrical and thermal conductivity [28]. Defect-free graphene has therefore been reported to have a thermal conductivity between 4500 and 5200 W/m·K [28]. Additionally, graphene exhibits an ultra-high electron mobility (25 × 10⁴ cm²/ V·s) and an electrical conductivity of 10⁴ S/cm [29] (**Table 1**).



Abbreviations and symbols: GBNs – Graphene based nanomaterials; GO – Graphene oxide; rGO – Reduced graphene oxide; GQDs – Graphene quantum dots; n/a – not available; NIR –near infrared; E – Young's modulus; FS – Fracture strength; κ – Thermal conductivity; σ – Electrical conductivity.

Table 1.

Summary of the properties of the family of graphene nanomaterials.

Defects caused by GO and rGO manufacturing lead to disruption of graphene sp² bonding orbitals and the addition of abundant surface groups that impede electron and heat flow, thereby reducing electronic and thermal conductivity of these GBNs [10, 40]. However, the electrical conductivity can be greatly improved upon GO reduction and conversion into rGO, although it is always smaller than that of graphene, as even after reduction, the rGO contains residual sp³ bonded carbon to oxygen, which interferes with the electron movement through the rest of the sp² clusters [10, 40, 41].

As a result of its superior electrical conductivity and thermal properties, graphene is the nanomaterial of choice for electronic applications, but also for biomedical applications for cell potential assessment and as a substrate for biosensors and conductive cell culture devices [42–45].

3.3 Physicochemical properties

The first special physicochemical characteristics of graphene are its high surface area combined with the sp² network (**Table 1**). These two characteristics confer great reactivity to graphene. The graphene planar and electron networks can engage in various electrophilic replacement reactions such as click reactions, cycloadditions, and reactions to carbine insertion. Moreover, the sp² network enables π - π stacking interactions with aromatic structures existent in therapeutic agents, or biomolecules [26]. Finally, pristine graphene has a water contact angle of 95–100° [46] indicative of a hydrophobic nature, which means that therapeutic agents may also establish hydrophobic interactions with graphene via van der Waals interactions. The problem with the extreme hydrophobicity of graphene is the difficulty of dispersing it in aqueous media requiring the use of surfactants or other stabilizing agents to avoid agglomeration in biological fluids [10].

GO preserves unmodified areas of graphene, which are hydrophobic and capable of establishing π - π interactions adequate for drug loading and non-covalent functionalization. However, it can be said that GO has a higher loading potential as it has additional epoxide and hydroxyl groups (**Table 1**) capable of forming hydrogen bonds and weak interactions with other groups of the therapeutic agents [47]. In addition, GO has an amphiphilic nature, since it possesses other oxygen functionalized groups that are ionized at certain pH values (e.g. carboxyl groups are negatively charged at pH values greater than \approx 4.5) [48]. The presence of ionizable groups and negative charges enhances the reactivity of GO, as additional electrostatic interactions can be established with therapeutic agents. Moreover, charged groups also reduce the water contact angle of GO to 30.7°, improving aqueous solubility and consequently improving colloidal stability [10, 40, 48]. In contrast, rGO (**Table 1**) contains higher number of defects that occurred during GO oxygen removal making it less hydrophobic than graphene (but more hydrophobic than GO) and less reactive than GO [41].

In conclusion, the physicochemical attributes of graphene and rGO make these materials suitable for the loading and delivery of hydrophobic or aromatic bearing therapeutic agents, but their hydrophobic nature creates problems of colloidal stability. In the context of the loading and delivery of therapeutic agents, GO is the GBN that reunites the best physicochemical features: large surface area; capacity of establishing π - π interactions, hydrogen bonds, hydrophobic interactions and electrostatic interactions; amphiphilic nature and colloidal stability [8, 10, 40].

3.4 Optical properties

In terms of electronic transitions, pristine graphene is considered to have a zero-band gap, i.e., no distance between the valence band and the conduction band [49–51]. This property makes graphene an outstanding electron conductive material, but a material that is unable to reach electronic excited states capable of optical excitation and visible emission. Pristine graphene is also a low-absorption nonphotoluminescent material with a 97.7% light transmittance of the total incident light across a wide range of wavelengths [30]. Defect-free or unmodified graphene is therefore not completely suitable for biomedical imaging as its light absorption and optical image contrast are poor. In addition, only when the size of the graphene is reduced to a nanoscale (e.g., in the case of GBNs) can photoluminescence be caused by an increase in the bandgap. In this regard, GO and GQDs are more interesting for biomedical imaging applications due to their intrinsic photoluminescence [49–51]. The bandgap changes that occur during GO reduction decreases rGO photoluminescence capacities.

The origin of GBNs photoluminescence is still widely discussed and not completely elucidated, but three mechanisms have been proposed to explain this property [49–51]:

3.4.1 Quantum confinement effect

In the GBNs structure, the photoluminescent properties are determined by the confinement effect of the π and π^* electronic levels sites of the sp² clusters determined by the bandgap of σ and σ^* states of the sp³ matrix. Upon excitation, an electron from the valence band is promoted to the conduction band leaving a hole behind after absorbing a photon with higher energy than the band-gap energy [50]. This causes the formation of an exciton (a state of excited electron, also referred to as electron–hole pair). When the exciton returns to a lower level this results in the emission of fluorescence [50].

The natural separation distance between the positive charge (hole) and negative charge (electron) in the exciton is designated as the Bohr radius. If the size of the nanomaterial is smaller than the Bohr radius, there will be an electron confinement effect. Excitons have an infinite Bohr radius in graphene. Thus, GBNs, being graphene fragments of any size, will have a quantum confinement effect and, consequently, a photoluminescent effect [50]. GBNs also have a size-dependent photoluminescence as the space between the energy levels (bandgap) can be tuned to the lateral size of the nanomaterial. Smaller sizes have larger band gaps and emit at lower wavelengths, while larger ones have smaller band gaps and emit at higher wavelengths [50].

3.4.2 Surface state

Changing the surface state by the presence of impurities, defects or surface functionalization causes the formation of trap states, i.e., the exciton can be trapped under these conditions leading to a lower-energy radiative emission resulting in a red-shift emission [49–51]. This is what happens, for example, in oxidative graphite exfoliation processes to obtain GO, a process that induces the functionalization of the surface with oxygen functional groups, reducing the band gap energy and therefore causing fluorescence emission at higher wavelengths. This strategy can be used to enhance fluorescent emission in the near infrared (NIR) region known as 'biological window' where the autofluorescence from haemoglobin and biological tissue is negligible and therefore the signal-to-noise ratio can be improved [49–51].

Another proposed mechanism to change emission properties and produce a more emissive material is the creation of conjugated π domain upon a careful choice of the surface functionalization [49–51].

3.4.3 Edges

Depending on the chemical structure of the GBNs edges different emission can be obtained: carbene-like edges have a zig-zag conformation that reduces the band gap energy resulting in a red-shift emission, whereas carbyne like armchair conformation increases the band gap energy resulting in a blue-shift emission [49–51].

Other important optical property that has been exploited for biosensing is the GBNs ability to act as efficient fluorescent quenchers for a variety of fluorophores through nonradiative electronic fluorophore-to-GBN energy transfer.

Finally, a fundamental optical property is the capacity of graphene and its GBNs derivatives to have strong absorption in the NIR range, which means that these nanomaterials are capable of converting photons into heat by NIR irradiation, making them powerful agents for photothermal therapy [52]. In this matter, the reduction of GO to rGO in order to partially restore the aromatic, conjugate character of the graphene sheets increases the absorption of NIR by >6-fold [36].

4. Synthesis of GBNs

Despite the enormous increase in the number of literature studies on graphene synthesis, the large-scale commercial development of graphene is still difficult to achieve [35]. Indeed, the development of cost-effective, highly reliable and scalable synthesis processes with high product yields and quality is a major challenge [35, 53]. In this chapter we will briefly present the methods to synthesize GBNs categorizing these methods in classical and green methods.

4.1 Classical methods

The classical methods (**Figure 1**) used in the synthesis of GBNs can be classified into two categories: top-down and bottom-up [35, 54].

4.1.1 Top-down methods

Top-down methods of GBNs' synthesis start with graphite or other carbon sources such as carbon nanotubes, fullerenes or larger graphene sheets that are cut into smaller monoatomic carbon pieces. These methods may be mechanical, chemical, or physical [55].

One of the most famous mechanical methods is the exfoliation of graphene from graphite firstly described by Geim and Novoselov [1]. This method is remarkably simple and consists of repeatedly gluing a graphite flake with adhesive tape and sticking it and peeling a dozen times [1, 56]. This process can cut a 1 μ m thick graphite flake into a single-layer, thin graphene sample that is afterwards transferred to a clean substrate (Si/SiO₂) by gently pressing the tape. Post-heat treatment may be used to remove residues of glue from the tape [37].

Chemical methods range from oxidation processes to other nano-cutting strategies using electrochemical or hydrothermal/solvothermal special oxidation. Oxidation may be handled by a one-or two-step method. The first step uses oxidizing agents (e.g., nitric acid, sulphuric acid, potassium chlorate, potassium permanganate) to oxidize graphite-based materials using the Hummer method or a modified version of the Hummer method [35, 54]. Graphite oxidation breaks the sp² hybridized carbon sheets into a graphite sp² domain surrounded by sp³ domains and several defects. Oxidized graphite is a stacked structure similar to graphite, but with a wider spacing between graphite sheets and several oxygen functional groups



Figure 1.

Classical methods for the synthesis of Graphene-based Nanomaterials (GBNs). Abbreviations: CVD – Carbon Vapor Deposition; GO – Graphene Oxide; rGO – reduced Graphene Oxide; UV – Ultraviolet light.

[35, 54]. In the second step, the oxidized graphite is exfoliated in GO sheets or in smaller parts such as GQDs using mechanical forces in aqueous solutions (sonication and centrifugation) [35, 54]. After obtaining GO sheets, it is possible to remove some of its oxygen functional groups by converting GO to rGO. This can be accomplished by thermal and UV treatment of GO or by chemical reduction using hydrazine, ascorbic acid, sodium borohydride, or hydroquinone [35, 54]. Electrochemical techniques include using chemical agents to assist in the growth of carbon electrodes. Carbon electrodes are broken up by electrochemical cutting, allowing for GBNs to be produced. The applied electric field draws the carbon particles from electrodes through graphite layer intercalation and radical reaction [55]. On the hydrothermal/ solvothermal oxidations defect-based carbon materials as GO and carbon nanotubes are cut under high temperature and pressure due to the action of strong alkaline medium. Some special photo-Fenton reactions may also break up GO to form GQDs. Among the physical methods of synthesis, arc discharge, laser ablation or reactive ion etching (RIE) nanolithography are the most widely used. RIE is one of the most efficient for controlling the size and chemical surface of GQDs and is also favorable for the study of some photoluminescent mechanisms [55].

4.1.2 Bottom-up methods

Bottom-up methods are based on the use of simple carbon molecules to build more complex structures such as graphene. These methods include the epitaxial growth of graphene layers on metal carbides by sublimation or by chemical vapor deposition (CVD) directly on metal surfaces [37]. It also includes organic synthesisbased methods in which intramolecular oxidative reactions using polycyclic aromatic hydrocarbons (PAHs) are widely used. Among the bottom-up methods, CVD

is the most widely used as it enables low-cost, large-scale production of high-quality materials [37, 55]. The main disadvantages of this method are the high toxicity of the chemical reaction by-product and the need for a fine choice of precursors. CVD production of graphene sheets occurs mainly in two stages [37, 55]. In the first step, the precursor (carbon containing gas) is injected into the reaction chamber. The chamber is subjected to high temperatures and the gas is pyrolyzed inside the chamber to obtain dissociated carbon atoms. This stage must occur on the surface of the substrate to avoid precipitation of carbon clusters during the gaseous phase [37, 55]. The second stage occurs due to the precursor's pyrolysis and corresponds to the deposition of a single atomic layer on the substrate. After the deposition and diffusion of the desired material on the substrate, the by-products dissociate from the substrate and are pumped out of the chamber [37, 55].

Bottom-up methods of synthesis are considered time-consuming and face challenges, therefore focusing on top-down methods that generate GO and rGO are more popular, particularly for the use of GBNs in theranostic applications [54].

4.2 Green methods

As a new category of carbon materials, GBNs have attracted considerable attention due to their tunable photoluminescent properties, low toxicity, strong biocompatibility and excellent photostability [8]. However, despite their general use, standard GBNs' synthetic methods are generally expensive [57], complex and require toxic reagents [58]. The biocompatibility of the carbon content of GBNs may therefore be compromised by the toxicity associated with their classic production methods. Alternatively to classical approaches, GBNs' green approach synthesis, for example, by substituting chemical reducing agents for natural products, is a promising and fascinating field where the resulting material and synthetic processes are biocompatible and can be more safely integrated into living systems for bioapplications [59]. It is therefore important to invest in more sustainable, environmentally friendly, and biocompatible techniques.

Nowadays, various green methods have been reported with interesting applications to produce GBNs alone or conjugated with other substances that enhance their bioactive effect. For example, most of the chemical methods used to date to produce graphene include harsh oxidizers and organic solvents, all of which are environmentally hazardous [60]. Alternatively to chemical methods, green graphene synthesis can be performed by electrochemical exfoliation of graphite into graphene sheets using a molten salt mixture. The molten salts are environmentally friendly and allow the interaction of alkali ions with graphite, which enables the formation of graphene nanosheets and flakes. In addition, this process reduces the number of defects in the graphene structure compared to classic chemical-rich processes [60].

GO's synthesis using classical methods is also very harmful to the environment. For example, in the Hummers method, approximately 1000 times more water than graphite must be used to remove excess oxidants after oxidation reactions, resulting in a large amount of wastewater containing mixed acids and heavy metal ions typically detected on GO sheets [61]. In addition, these methods are all timeconsuming, and take a few to hundreds of hours of oxidation. The oxidation time can be shortened to around 1 h simply by using stronger oxidizing mixtures that contribute to further contamination [61]. An alternative green approach to these classical methods is the electrolytic oxidation of graphite water. The GO obtained shows similar chemical composition, structure, and properties to those accomplished by the classical Hummers method and enables ultra-fast oxidation of the graphene lattice within a few seconds, which is more than 100 times faster than currently available methods [61]. The classical synthesis of rGO poses the same problems. The most used reducing agents, such as hydrazine, dimethylhydrazine and sodium borohydride, are highly toxic and remaining trace amounts of these toxic agents can have harmful effects, especially for bio-related applications [62]. In addition, the handling of hazardous waste produced by GO's reduction reaction to the production of rGO may dramatically increase costs on an industrial scale. Efforts have been made over the past few years to counteract toxicity issues by using natural reducing agents [62]. For example, plant extracts (aqueous leaf extracts of *Colocasia esculenta*, *Mesua ferralinn*, *Citrus sinensis*, tea polyphenol [62–65]), microorganisms (bacteria and baker's yeast [62, 66]), amino acids [67], bio-antioxidants (melatonin) [68], non-harmful acids (hydriodic acids, trifluoracetic acid), glucose and glucosamine [62, 69] are used as green reducing agents. Although the degree of reduction of GO by these strategies is typically lower than that of the hydrazine–based method, the excellent biocompatibility of the obtained rGO sheets may enhance their ability to be used in biological and biomedical fields [62].

Preparative methods of GQDs, which are typically manufactured with strong acids or organic solvents, often face severe challenges, and post-treatment with complicated methods remain necessary. Thus, raw materials made from natural renewable resources should be identified, as well as separation and post-treatment procedures that can be performed without complicated processes and without heavy/polluting waste generation [70]. For example, GQDs were synthesized using cotton cellulose, where cellulose and water were part of the reaction mechanism, in the absence of all other dangerous and chemical materials [71]. In another study, GQDs were synthesized by an organic solvent-free methodology using only deionized water and glucose as a precursor [72]. Microwave-assisted synthesis is another technique that has been reported to be able to produce, for example, carbon quantum dots in one-step using roasted chickpeas as carbon source [73] and also aqueous soluble GQDs using cow milk [73]. In another study, GQDs were produced by a simple, eco-friendly and single-pot hydrothermal reaction, with starch as a precursor [74]. In addition, a simple and high-yielding hydrothermal method has been reported to produce GQDs from glucose [75]. GQDs have also been produced using coal tar pitch, a by-product of the coking industries, oxidized with hydrogen peroxide under mild conditions [76]. Finally, also using hydrogen peroxide under mild conditions it is possible to produce GQDs by a greener hydrothermal synthesis using GO as precursor and without involving any harsh reagents [77].

In conclusion, green synthesis of GBNs is an essential area of research that should be promoted within the scientific community once it presents many advantages: (a) it is inexpensive and renewable precursors are easily obtained; (b) it is environmentally-friendly, once no hazardous reagents are needed; (c) it involves simple methods, usually in one-step or one-pot; (d) normally avoids any complicated post-processes [71]; (e) originates products with great biocompatibility [72].

5. Applications of GBNs in therapy and diagnostics (theranostics)

As described earlier, the interesting properties of GBNs have placed these nanomaterials as ideal for creation of theranostic strategies particularly used in the therapy and therapy monitorization (diagnostic) of cancer [8]. Current treatments involve several variations of different strategies that can be used for therapeutic and diagnostic ends. Because each strategy has various inherent advantages and different mechanisms of actuation, a mixture of complementary strategies may result in a synergistic effect. **Figure 2** presents a schematization of the main therapeutic and



Theranostic strategies of Graphene-based Nanomaterials. Abbreviations: CT—Computed Tomography; IR-TI—Infrared Thermal Imaging; MHT—Magnetic Hyperthermia Therapy; MRI—Magnetic Resonance Imaging; PAI—Photoacoustic Imaging; PAT—Photoacoustic Therapy; PDT—Photodynamic Therapy; PET— Positron Emission Tomography; PL—Photoluminescence; PTT—Photothermal Therapy; SERS—Super Enhanced Raman Spectroscopy; SPECT—Single Photon Emission Computed Tomography; USI—Ultrasound Imaging.

diagnostic strategies. The therapeutic and diagnostic strategies of GBNs will be presented together with some examples of their use in the following subsections.

5.1 Therapeutic strategies

5.1.1 Chemotherapy and gene therapy

The GBNs' intrinsic properties have paved the way for the advancement of approaches to chemotherapy and gene therapy.

Chemotherapy implies the use of anticancer drugs which, by several mechanisms (i.e., interfering with angiogenesis and cell division), may result in cellular damage/stress and may lead to cell death if apoptosis is triggered. The chemotherapeutic arsenal is widely known as it is the basis of classical cancer therapy [8]. Furthermore, by incorporating these drugs into nanocarriers like GBNs, the toxic effects of anticancer drugs in healthy cells that are not affected by cancer can be reduced [8]. Indeed, GBNs (especially GO) have a high drug loading ratio of hydrophilic and lipophilic anticancer drugs, due to the combination of a large surface area and the presence of delocalized π electrons, as well as chemical polar groups [8]. The diverse range of potential chemical interactions between anticancer drugs and GBNs has conferred to these nanocarriers an important role in chemotherapy, as drug loading ratios can exceed 200 wt%, which is unusually high compared to other nanocarriers [78]. For example, the commercial liposomal formulations Caelyx[®] and Doxil[®] containing the anticancer drug doxorubicin have a drug load of 16 wt %, while the majority of GBNs' formulations can meet the drug loading values from 55 wt % to 133 wt % [79-85]. GBNs loaded with another anticancer drug, paclitaxel, also achieved a remarkably effective drug loading of 90 wt % compared to commercial formulations containing this drug: Taxol[®] and Abraxane[®] with a drug loading of 1 wt % and 11 wt %, respectively [86].

Gene therapy requires the incorporation of genes, gene segments or oligonucleotides in nanocarriers that provide protection against enzyme-induced degradation and/or inactivation of the genetic material [8, 87]. When used in cancer, the mechanism of action of this therapeutic strategy is based on: (i) deactivation of oncogenes; (ii) substitution of non-functioning tumor suppressor genes; (iii) inducing cell death or repair of normal cell function; (iv) defense of normal cells from drug-induced toxicity or activation of immune cells for the destruction of cancer cells [8, 87]. The same favorable properties of GBNs for chemotherapy are valid for explaining their use in gene therapy. Indeed, GBNs have shown the ability to efficiently condense genetic material by π - π stacking interactions, avoiding endonuclease's degradation of nucleic acids [40, 88, 89].

5.1.2 Hyperthermia

Hyperthermia is a therapeutic strategy that causes the temperature rise to kill cancer cells. Mild hyperthermia (temperature rise to 43–50°C) induces increased membrane permeability, defective membrane transport, metabolic signaling disturbance leading to cell apoptosis. Extreme hyperthermia (temperature rise >50°C) causes necrotic cell death due to cell membrane disruption and protein denaturation [8].

The optical and thermal properties of GBNs make these nanosystems desirable for their use in the hyperthermia treatment of cancer cells. GBNs have a wide absorption in the NIR region (700–1100 nm) and can convert it into thermal energy causing local hyperthermia. At the same time, the hyperthermia effect can reduce GBNs' oxygen functional groups causing the release of gas. The formation and collapse of gas bubbles contributes to the development of a microcavitation environment often responsible for the death of cancer cells. Hyperthermia therapy strategy, based on the conversion of absorbed NIR to thermal energy, is known as photothermal therapy (PTT) [8, 90, 91]. Over the last 6 years, PTT has been the therapeutic strategy most explored by researchers working with GBNs [83, 92–97]. This is primarily because this strategy has the advantage of not needing cell internalization of GBNs while maintaining a deep penetration of biological tissues [8]. The efficacy of PTT to destroy cancer cells has also been improved by conjugation of GBNs with other narrow-bandgap materials [84, 85, 98–112]. Moreover, while GO has been the perfect GBN for chemotherapy and gene therapy, rGO is the preferred nanomaterial for PTT because it has an NIR absorption 6 times higher than GO [8, 113].

Another strategy to increase the death of cancer cells by hyperthermia is to combine magnetic hyperthermia (MHT) with PTT through conjugation of GBNs with magnetic nanoparticles (MNPs) [82, 113]. MNPs exposed to an external alternating magnetic field can convert magnetic energy into thermal energy by Néel or Brownian relaxation mechanisms. When the application of the magnetic field is faster than the relaxation time of the MNPs, the delay in magnetic moment relaxation induces MHT [8].

5.1.3 Photodynamic therapy

Recently, GBNs have also been applied to photodynamic therapy (PDT) strategy used to kill cancer cells [8, 52, 114]. This strategy requires a photosensitizer (PS) agent to be loaded into the GBNs by π - π stacking and/or hydrophobic interactions. Upon photon absorption, the PS agent will be excited to a singlet state after which it decays into a low-energy excited triplet state through intersystem crossing. Then, in the excited triplet state, PS transfers an electron to: (i) different molecules producing reactive oxygen species (ROS): $O_2^{\bullet-}$, H_2O_2 , HO^{\bullet} or (ii) oxygen originating ${}^{1}O_2$. ROS interact with cellular components of cancer cells (lipids, proteins, nucleic acids) causing oxidative stress and ultimately cell death [8, 52, 114].

PDT is commonly used in conjunction with PTT to benefit from the synergistic influence of both therapeutic strategies [101, 108, 115–124].

5.2 Diagnostic strategies

5.2.1 Photoluminescence

GBNs possess attractive optical features applied to the monitoring of therapeutic efficacy. As a result, GBNs act as dye-free labeling to follow the delivery of therapeutic nanosystems to cells. Due to the quantum confinement effect that exists when the sizes of GBNs are smaller than their exciton Bohr radii, the nano-sized material has non-blinking photoluminescence (PL) and photostability [8]. GBNs therefore emit low-energy fluorescence when excited by high-energy light (usually UV or visible light) and GBNs' fluorescence intensity remains strong under confocal laser lighting. GQDs are among the most used GBNs for their PL [88, 89, 99, 115, 125–129].

Upon conjugation of GBNs with upconversion luminescence nanoparticles (UCNPs), such as: NaYF₄:Yb³⁺, Er³⁺ or NaYF₄:Yb³⁺, Tm³⁺ an anti-Stoke emission occurs when two or more low-energy photons from NIR light are absorbed to generate higher energy emissions in the visible region. The conjugation with UCNPs confers to GBNs an even more fascinating PL property, as in this case excitation with NIR light produces emission at lower wavelengths. The advantages of this upconversion PL are due to the use of NIR light excitation, which reduces autofluorescence of biological tissues and increases penetration depths, thus reducing photo-damage of healthy tissues [8, 95, 101, 121, 124].

The fluorescence quenching capability demonstrated by GBNs resulting from fluorescence resonance energy transfer (FRET) or non-radiative dipole–dipole interactions between fluorescence species and GBNs is also important. The fluorescence quenching effect is used as an external diagnostic feature that enables the release of GBNs' cargo to be identified [8]. Indeed, when GBNs interact with fluorescent cargo (drugs or other active substances) they reduce their fluorescence emission, but when the cargo is released, the fluorescence emission is reset [79, 130].

5.2.2 Infrared thermal imaging

Infrared thermal imaging (IR-TI) is a diagnostic strategy based on thermal changes due to radiation absorption. Light absorbed and not lost by emission results in heat that can be registered as an image [8]. As a result, the GBNs photothermal conversion properties used in PTT can also be used as a therapy-guiding strategy under an IR-TI non-labelling technique. The use of the NIR laser to trigger a PTT effect can be detected by means of a visible thermal field signal, which is especially important because of its non-invasive nature and because it provides real-time images [8]. Provided that PTT is one of the treatment modalities most commonly used by GBN-producing researchers for biomedical applications, IR-TI is also widely used, as both strategies (PTT and IR-TI) are often used together [92–99, 105–108, 110, 112, 113, 119, 120, 124, 131–133].

5.2.3 Raman spectroscopy and surface enhanced Raman spectroscopy

Raman scattering-based spectroscopy can be used as a diagnostic technique to obtain morphological and chemical information from accessible tissue surfaces, e.g., skin, gastrointestinal tract, or intraoperatively. This imaging technique combines the surface imaging of the tissues with the Raman spectra provided by its molecular components [8]. When visible or NIR light interacts with the surface material it originates inelastic scattering of photons (Raman scattering) that display a shift in frequency. The energy shift provides information on the vibrational modes in the system. GBNs usually demonstrate the required Raman scattering intensity, exhibiting the standard D, G and 2-D band characteristics of the vibrational modes in the range 1000–3000 cm⁻¹. As a result, the delivery of GBNs used as cancer therapeutic tools can be followed by Raman imaging of the tissues [8].

Raman imaging is an even more effective diagnostic strategy when GBNs are associated with gold and silver nanoparticles. In this case, the Raman signals of GBNs are significantly improved by the surface enhanced Raman scattering (SERS). Indeed, SERS occurs when molecules are adsorbed or located near a metallic nanostructure, i.e., the improvement of the Raman scattering occurs due to the resonant interaction of light with the surface plasmons that are excited at the surface of the metallic nanostructure. Using this strategy, SERS can be used to combine microscope cell imaging with Raman spectroscopy, mapping the presence of GBNs in the tumor tissue of the cell [8, 103].

5.2.4 Ultrasound Imaging

Using the electrical properties of GBNs, it is possible to image these nanosystems in their journey through the body using ultrasound imaging (USI) strategies [96, 102]. USI is therefore based on the conversion of electrical signals to ultrasound waves that penetrate the body and biological tissues. Some of these ultrasound waves are reflected and transformed by a transducer into electrical signals that are handled and displayed as an image [8].

5.2.5 Photoacoustic imaging

Photoacoustic Imaging (PAI) is another diagnostic strategy that benefits from the NIR absorption capacity of GBNs and enables monitoring their distribution in body tissues. When tissues are irradiated with NIR short laser pulses, locally dispersed GBNs absorb energy and generate heat that leads to thermoelastic expansion followed by contraction and consequent emission of mechanical pressure waves at ultrasonic frequencies [8]. Periodic sound waves produced can be sensed by ultrasonic transducers creating an image by mapping the original absorbed energy distribution [8]. Among the GBNs, rGO has gained interest as a PAI contrast agent due to its higher NIR absorbance properties [85, 96, 125, 134]. In spite of the improved PAI properties of rGO, GO nanomaterials compensate for their lower NIR absorption with higher loading capacity. In some studies, thus, GO nanomaterials were loaded with other narrow-band gap materials as a solution to increase NIR absorption and thus also attained PAI diagnostic modality [80, 100, 105, 110].

5.2.6 Tomography

Tomography is a nuclear medicine imaging technique where a cyclotron is used to produce short or ultra-short-lived radionuclides that decay with the emission of: (i) positron, in the case of Positron Emission Tomography (PET); (ii) γ rays in the case of Single Photon Emission Computed Tomography (SPECT); and multiple X-rays in the case of Computed Tomography (CT). All these techniques rely on differential levels of the radiation attenuation within the body to create threedimensional, high-contrast anatomical images that allow for delineation between various structures [8].

The physicochemical properties of GBNs promote the loading of these nanocarriers with radionuclides that enable tomography imaging of tissues [85, 102, 124, 132].

5.2.7 Magnetic resonance imaging

Magnetic resonance imaging (MRI) consists of the application of radiofrequency pulses and is derived from the interaction between the water protons and the magnetic field applied. The resulting image is produced by the pattern of absorption and emission of the electromagnetic wave [8]. In order to increase the visibility of anatomical structures, contrast agents (MRI probes) are used to reduce the relaxation times of water protons inside body tissues [8]. The unusual wide surface area and high loading capacity of the GBNs have also proven to be very advantageous for carrying MRI probes [81–83, 113, 124, 130]. In addition, the high molecular weight of GBNs can reduce the rotational motion of the water proton, increase the relaxation time and increase the *in vivo* half-life of the MRI contrast agent, resulting in a better image [113].

6. Application of GBNs in bioremediation

GBNs offer a holistic approach to health. In fact, in the previous sections, we described the great potential of GBNs in human health due to their role in therapy and diagnosis. Moreover, GBNs or their functionalized derivatives are cutting-edge materials used in bioremediation, and their remarkable properties can be used to mitigate environmental contaminants, as well as to improve human, plant, and animal health [17–20, 25, 135].

The following sections describe the properties of GBNs that favor their use in bioremediation and the major pollutants on which GBNs have demonstrated their bioremediation efficiency.

6.1 GBNs properties and processes involved in bioremediation

Graphene oxidation to GO and rGO reinforces its properties and improves its hydrophilic nature, thereby enhancing its ability to associate with contaminants either physically or chemically. This association can be processed by adsorption of contaminants on the surface of GBNs or by the oxidation breakdown of contaminants, by photocatalysis or other advanced oxidation processes (AOPs) [18].

6.1.1 Adsorption

One of the most widely used processes for bioremediation is chemical and physical adsorption. The adsorption capacity of materials depends on several characteristics [25]:

- i. good mechanical strength for handling and possibly regenerating and reusing;
- ii. strong wettability to ensure use in the adsorption of water pollutants;
- iii. high porosity in favor of physical adsorption;
- iv. large surface area and different functional groups to promote chemical adsorption.

As previously described GBNs obey to all these requirements and hold great potential as adsorbent materials. GBNs have a large surface area and excellent mechanical properties. GBNs also have favorable wettability and different functional surface and edge groups (in these aspects GO has more adsorbent properties than rGO) [18]. As far as porosity is concerned, highly porous GBNs have recently been developed by chemical activation of GO precursors with KOH [25]. Other GBN derivatives functionalized with metal/oxide composites or magnetic nanoparticles may also improve the adsorption capacity of GBNs or demonstrate advantages in the magnetic separation of contaminants adsorbed and re-use of adsorbents by adsorption–desorption cycles [20, 25, 135]. GBNs can also be functionalized with chelating compounds like ethylenediamine tetraacetic acid (EDTA) which favors adsorption of metal ions [19]. However, while the functionalization of GBNs may improve the adsorption capacity of some specific contaminant, it may also limit its use for a more generic type of adsorbate [20].

With regard to the chemical versatility of GBNs, this material is certainly advantageous in comparison with other adsorbents [15, 19, 20]. For example, GO has oxygen-functionalized groups (e.g., COOH) which are deprotonated at a broad range of pH values (\approx pH > 4.5) and therefore negatively charged groups establish electrostatic interactions with cationic pollutants [19]. Oxygen-functionalized groups also enable hydrogen bonding with adsorbate compounds. These interactions may be established between hydrogen with a partial positive charge and an electronegative atom such as chlorine, fluorine, or oxygen [20]. Hydrogen bonding can therefore be formed between hydrogen atoms present in the functional moieties of GBNs and partially negatively charged atoms of the adsorbate molecule [20]. Hydrophobic interaction is driven by the entropic effect that occurs when ordered water molecules are banned from nonpolar carbon surface of GBNs. Hydrophobic interaction is also another significant contribution to the adsorption of hydrophobic/amphiphilic contaminants to GBNs [19]. Finally, GBNs have the possibility to establish π - π interactions with aromatic rings from contaminants, which may be the only interaction established or may be strengthened by simultaneous electrostatic interactions in cases where aromatic contaminants are also charged [19, 20].

Figure 3 illustrates the possible adsorption mechanisms of the different pollutant compounds on GBN adsorbents.



Figure 3. Common chemical interactions established between Graphene-based Nanomaterials and pollutants.

6.1.2 Oxidation and photocatalysis

GO-presenting oxygen functional groups also lead to redox reactions and make different contaminants environmentally friendly and degradable [18]. This removes the problem of waste management that exists in the case of adsorption. Radicalbased oxidation processes, also referred to as AOPs, specifically turn organic entities into environmentally compatible harmless entities, including various minerals, less toxic fragments of carbon-based contaminants, and neutral entities such as water and carbon dioxide [18]. Photocatalysis is also an AOP that is effective in the degradation of various organic pollutants by GBNs and their composites. GBNs with a zero-band gap are capable of absorbing light over a wide spectrum. This allows the electrons to be excited from the valence band to the conduction band, forming holes in the valence band. Both electrons and holes are involved in redox reactions that produce many radicals (e.g., hydroxyl radicals) [18]. These radicals serve as potent oxidizers across the surface of GBNs and are responsible for photocatalysis of organic contaminants enabling the destruction of dyes and other organic matter from wastewater [18]. It is also helpful to reduce the band gap of GBNs by loading them with materials such as titanium (TiO_2) and zinc oxide (ZnO) to allow efficient use of solar irradiation during photocatalytic decomposition [17].

6.2 Atmospheric pollutants

6.2.1 Gas pollutants

Gas pollutants have risen over decades due to industrial developments and have become one of the most significant issues in the modern world. Because of its widespread combustion from vehicles, forest fires and manufacturing processes, CO_2 is the air pollutant of most concern [20]. The ability to block infrared irradiation in the stratospheric layer exacerbates the greenhouse effect and, thus, global warming [20]. Chlorofluorocarbon (CFC), a gas used in freezers, refrigerators, and air-conditioners, is another chemical specie which causes serious damage to the atmosphere. CFC has the property of interacting with ozone causing damage to the ozone layer, responsible for filtering UV irradiation from sunlight [20]. Inorganic gaseous pollutants such as SO_2 , NO_2 , NH_3 and H_2S are also implicated in the phenomenon of acid rain [20, 25]. Monuments and buildings damage, flora degradation, a reduction in soil pH, pollution of the bodies of water and human diseases are the environmental effects of acid rain in large cities; however, it is very difficult to measure them economically [20]. In addition, possible health hazards such as respiratory irritation and damage to the central nervous system have been associated with long-term exposure to these contaminants [20].

GO and other GBNs as well as their modified forms are good adsorbents for the reactive removal of these toxic gases. Most of the research, however, concentrated on NH₃ adsorption using GBNs and composites modified by metal oxide. Owing to the presence of diverse active defect sites, such as the hydroxyl and epoxy functional groups and their neighboring carbon atoms, NH₃ adsorption on GO is usually greater than that on other GBNs [25].

6.2.2 Volatile organic compounds

A wide number of volatile organic compounds (VOCs) are responsible for the growth of cancer in people all over the world, according to the WHO [20]. Formal-dehyde which comes from paint and decorating materials, is one of VOCs and the major indoor air pollutant responsible for the sick building syndrome [25].

In order to reduce harm to the environment and human health caused by VOCs, GBNs, in particular GO, have recently been employed in several studies for VOC removal by adsorption and photocatalytic decomposition [20, 25].

6.3 Water pollutants

One of the long-lasting concerns in the past few decades has been aquatic contamination due to industrial activities. Groundwater, surface water and wastewater systems contain many pollutants [14, 17, 20, 25]. Anions and heavy metal cations as well as organic compounds are significant contaminants (e.g., dye from textile factories, pesticides, and pharmaceuticals) [14, 17, 20, 21, 25]. Aqueous pollutants arising from waste oil from numerous oil leakage incidents and eventually from biological contaminants may also be identified [17, 20].

6.3.1 Inorganic metals and metalloid cations

Owing to their high toxicity to plants, animals and human beings, heavy metals are the most substantial contaminants in water. The most prevalent heavy metals in contaminated waters are Hg, Pb, Ag, Cu, Cd, Cr, Zn, Ni, Co and Mn [21, 25]. Most metal ions are found in cationic forms, but certain metals are present in anions such as Cr (VI) within CrO_4^{2-} , $Cr_2O_7^{2-}$ [21, 25]. The most important metalloid ion with high toxicity is arsenic present in the form of As (V) in $H_2AsO_4^-$ and $HAsO4^{2-}$ [135]. Arsenic is frequently present in soils and rocks in the form of minerals that are mobilized into groundwater by natural weathering, geochemical reactions, biological activity, volcanic emissions and industrial activities [135]. The high degree of exposure to arsenic by water is a calamity for developing countries. More than 100 million people from densely populated countries, including Bangladesh, China, India, Pakistan, Taiwan, and Mexico, and more than 70% of people from Asian continents, live at risk of arsenic-contaminated ground water and are drinking potable water contaminated with excessive levels of arsenic [25]. Huge amounts of adverse problems are caused by exposure to elevated concentrations of arsenic from drinking water and are commonly associated with skin lesions and hyperkeratosis as adverse effects, whereas long-term exposure leads to cancers of the skin, kidneys, liver and prostate. In addition, arsenic also affects nervous and cardiovascular system functions [25, 135].

Adsorption is probably the most efficient way to eliminate aquatic heavy metal ions, because bioprocessing and chemical reactions like photocatalysis are unable to destroy the metal ions. Due to the numerous functional groups on the surface, GO is a potential adsorbent for metal ion complexation by both electrostatic and coordination methods (e.g., upon GO functionalization with EDTA) [25]. Arsenic removal has become imperative, but most treatment processes are expensive, except for adsorption, which is affordable, convenient and easy to handle. For water treatment, GO and its composite-based membranes, thin films, paper-like materials, and solid composite materials have gained notoriety and have shown efficient and high potential for arsenic removal [135, 136]. The numerous oxygen functional groups are responsible for both higher adsorption and desorption potential of GO. With a change in solvent pH, arsenic desorption from the GO surface contributes to GO regeneration, which can be used to repeat adsorption-desorption processes, thus increasing adsorption efficiency and reducing costs [135]. The adsorption capability, selectivity, thermal and chemical stability of GO can be enhanced by surface modifications. Moreover, conjugation of GO with magnetic nanoparticles also facilitates the magneto-responsive separation of depleted adsorbents from water [135].

6.3.2 Inorganic anions

Some inorganic anions, F^- , NO_3^- , SO_4^{2-} , ClO_4^- , PO_4^{3-} , are still found in large amounts in water, and they may also cause water pollution and should be removed, although they are less harmful than heavy metal ions [25]. The presence of large amounts of NO_3^- and PO_4^{3-} , in water, for instance, can induce eutrophication (i.e., water enriched with nutrients that induce excessive growth of algae). Due to the negative anion charge, GO is not so successful for inorganic anion adsorption [25]. GBNs and functionalized GBNs, however, have been identified as efficient in inorganic anion adsorption. For example, the surface exchange between F^- in solution and hydroxyl ions promotes the adsorption of these anions to GBNs [25, 137].

6.3.3 Organic pollutants: dyes, polycyclic aromatic hydrocarbons, pesticides, and pharmaceuticals

Dyes are a class of organic compounds commonly found as water contaminants that are released from a wide variety of sources, such as printing, textiles, dyeing, paper production, tanning, and painting industries. Most dyes are durable and difficult to biodegrade and have complex molecular structures. By altering the color of water, the presence of dyes in water causes disturbance of the photosynthetic phase of aquatic plants, thus suppressing sunshine, creating an imbalance in the entire aquatic environment [18, 25]. In addition, certain dyes are detrimental to human beings. Most dyes are dissolved in water and are either cationic or anionic. By establishing electrostatic interactions, GO exhibits high adsorption of cationic dyes, but between GO anionic groups and anionic dyes, there is strong electrostatic repulsion. However, because of additional π - π stacking interactions, GBNs and composites can still be excellent adsorbents for cationic and anionic dyes [18, 25].

Another class of organic pollutants composed of repeated aromatic ring structures is polycyclic aromatic hydrocarbons (PAHs) [18]. They are non-charged and non-polar molecules produced from different methods, such as petroleum products burning, incomplete biomass combustion, coal mining [18], etc. PAHs have adverse effects on human health and are believed to cause cancer of the skin, blood, bladder, liver and cardiovascular diseases [18]. Owing to insufficient waste management, leakage and accidents, monocyclic aromatic hydrocarbons such as toluene, xylene, benzene are also largely excreted from industry causing damage to the human central nervous system [18].

Many pesticides are organic aromatic compounds still commonly used in agriculture, dairy, and insect control. In addition, pesticides have also been used in domestic gardening and veterinary practice by common citizens. Therefore, the systematic usage of pesticides is of concern owing to their neurotoxicity, carcinogenic potential and involvement in other pathologies [20, 138]. Moreover, the toxicity of organophosphorus pesticides lies in the fact that these compounds are inhibitors of acetylcholinesterase enzymes, which contribute to dysfunction of the nervous system [20].

Pharmaceutical drugs are also organic contaminants that have harmful effects on the environment and human health. Even at low concentrations, these chemicals are very difficult to remove and between 30 and 90% remain undegradable and are excreted as active compounds in the environment [20, 135].

Numerous investigations have demonstrated potential in the use of GO and other GBNs for the adsorption of PAHs, phenolic compounds, pesticides, and pharmaceutical drugs [20, 21, 25, 39, 135, 138]. In general, there are five potential interactions, including hydrophobic effects, π - π stacking, hydrogen bonds, and covalent and electrostatic interactions, which are assumed to be responsible for the

adsorption of organic compounds on the GBNs' surface [15, 19, 20, 25] (**Figure 3**). In the case of GO and other GBNs, the majority of investigations have shown that π - π association plays an important role in the adsorption of aromatic organic contaminants [25]. In comparison, the latest major methods used to treat these pollutants are AOPs and the chemical-microbial depletion [20].

6.3.4 Oil and its derivatives

The significant rise in the discovery of crude oil and the increase in the production of petroleum derivatives have caused negative and long-term destruction of various habitats [20]. One of the most important pollution issues happening very frequently in the ocean or seashore is oil leakage from reservoirs, ships, or oil drilling facilities. In order to minimize the harmful impact on marine ecology, the adsorption of leaking oils from polluted seawater has been an important area of study [17]. Latest experiments have successfully investigated the adsorption of oil emulsions on GBNs, demonstrating excellent adsorption capacities. Extremely porous GBNs (sponges, hydrogels and xerogels) are recently developed as cuttingedge oil adsorbents; many of them are conjugated with magnetic metallic nanospheres and typically have high recyclability [17, 20].

6.3.5 Biological contaminants

A significant process for public health safety is also the disinfection of the water supply and indoor air to remove common harmful pathogens, like bacteria (e.g., *E. coli*, *F. Solani*), and viruses (e.g., EV71 and H9N2 virus). In these cases, the use of GBNs together with UVC light is also effective for decontamination by photocatalysis [17].

7. Conclusions and prospects

In this chapter, the current progress on the use of various GBNs in the treatment of cancer and bioremediation has been reviewed. The extraordinary properties of GBNs have also been described with special focus in those that favor the biomedical applications of this material, i.e., the large surface area, the large number of unsaturated π -bonds, the mechanical strength, the NIR absorption properties, the PL capacity, etc. The versatility of GBNs is indicated as a feature that can be explored in the most diverse biomedical fields. In this sense, the use of GBNs in cancer theranostic strategies has been discussed. Successful research studies using GBNs for the loading of anticancer drugs or nucleic acids in synergistic chemotherapy, gene therapy and photothermal/photodynamic therapy have been revised in the field of cancer therapy. GBNs have also been described as imaging diagnostic tools used to track the path of therapeutic delivery in target tissues. Finally, the application of GBNs for photocatalysis and adsorption was described as a means of environmental decontamination, i.e., bioremediation.

It is clear from all the revised research that GBNs have a great future in biomedical applications, either as therapeutic tools or as bioremediation strategies, where specifically GO can be considered one of the most advanced and promising adsorbents. However, despite successful attempts to use GBNs in the biomedical field, there are still several challenges that need to be overcome prior to their widespread commercial or clinical use. First, green methods must be used to develop environmentally sustainable approaches to the production of GBNs. Some attempts at green synthesis have been made, but they are still far from proposing

standard and reproducible methods that can be scaled up to reduce production costs while maintaining a minimal presence of residual contaminants. In addition, although many studies have shown that GBN's adsorbents have been recycled, these studies are still scarce and more innovative research work needs to be explored in the future to achieve convenient separation and regeneration of GBN's adsorbents.

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Abbreviations

AOPs	Advanced oxidation processes
CFC	Chlorofluorocarbon
CSCs	Cancer stem cells
CVD	Chemical vapor deposition
СТ	Computed Tomography
EDTA	Ethylenediamine tetraacetic acid
FRET	Fluorescence resonance energy transfer
GBNs	Graphene-based nanomaterials
GQDs	Graphene quantum dots
GO	Graphene oxide
rGO	Reduced graphene oxide
IARC	International Agency for Research on Cancer
IR-TI	Infrared Thermal Imaging
MHT	Magnetic Hyperthermia Therapy
MNPs	Magnetic nanoparticles
MRI	Magnetic Resonance Imaging
NIR	Near infrared
PAHs	Polycyclic aromatic hydrocarbons
PAI	Photoacoustic Imaging
PAT	Photoacoustic Therapy
PDT	Photodynamic Therapy
PET	Positron Emission Tomography
PL	Photoluminescence
PS	Photosensitizer
PTT	Photothermal Therapy
RIE	Reactive ion etching
ROS	Reactive oxygen species
SERS	Super Enhanced Raman Spectroscopy
SPECT	Single Photon Emission Computed Tomography
UCNPs	Upconversion luminescence nanoparticles
USI	Ultrasound Imaging
VOCs	Volatile organic compounds
WHO	World Health Organization

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