Journal of Drug Delivery Science and Technology 84 (2023) 104446

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review article

Exploring graphene and its potential in delivery of drugs and biomolecules

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ARTICLE INFO

Keywords:
Graphene
Wonder material
Advanced delivery system
Biomolecules
Nanomedicine

ABSTRACT

Graphene hailed as the "wonder material" of the 21st century has achieved widespread advancements in various disciplines such as applied science and medical science. Due to its unique properties such as selectivity, greater medicament capacity, chemo-sensitization, and comfort of functionalization, extraordinary energy has been focused to explore its biomedical operation, particularly in chemotherapy, and in the development advanced delivery systems for drugs, biomolecules, and genes in the previous era. Graphene oxide, which may be coupled covalently or non-covalently with both hydrophilic and hydrophobic molecules, has also emerged as a key nano-vector because of its well-defined physicochemical features.Previously, several studies have been demonstrated that the functionalized form of graphene exhibits greater biocompatibility and could be a promising medium for the development of a novel transport mechanism, although few concerns remain their in vivo properties. This review focuses on graphene and its derivatives and their function in nanomedicine, in particularly the transport of drugs and biomolecules, as well as in the future trends and challenges associated with graphene-based materials.

1. Introduction

As a promising new scientific field, nanotechnology has the potential to revolutionize many areas of healthcare [1–3]. Compared with nano-materials derived from other elements on the periodic table, carbon-based nanoparticles have superior characteristics. Three types of carbon nanoparticles have garnered considerable interest. Carbon nanotubes, also called carbon filaments, were founded in 1991 with single-walled or multi-walled. Graphene is the newest form of elemental carbon. It is a sheet of sp^2-bonded carbon atoms arranged in a hexagonal pattern, similar to a honeycomb structure. Graphene is at the forefront of research in materials science and condensed matter physics [4,5]. It is the world's thinnest known material and act as basic building block for some other carbon-based materials. They can be rolled into one-dimensional carbon nanotubes (CNTs) and stacked into three-dimensional graphite. It can be wrapped in sphere-shaped fullerene by the addition of pentagons. It is the mother of all graphite materials [6,7]. Graphene and related materials currently represent the most advanced frontier in high-performance carbon materials, as demonstrated by the European Union Research Council imposing prospective activities known as EU Graphene Flagship. This effort aims to boost fundamental research on graphene and its associated chemicals to position the European Union as a global leader in the field. This was because of the superior properties of this allotropic, one-atom-thick, planar sheet of carbon firmly packed into a hexagonal cell structure. Even at very low concentrations, graphene can be used to improve the mechanical and electrical properties of composite materials made of both plastics and metals. Graphene and related materials are not expensive to be used and hence, are being used in high-value applications such as frontier medicine [7,8].

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https://doi.org/10.1016/j.jddst.2023.104446
Received 4 December 2022; Received in revised form 23 March 2023; Accepted 10 April 2023
Available online 11 April 2023

Most of the available conventional therapeutics and delivery systems are associated with various shortcomings such as abrupt metabolism and excretion of drugs before reaching the target site, poor aqueous solubility, non-specific to target site, and an opposing action on standard tissues. Several studies have revealed that such issues and challenges may be encountered when utilizing nanotechnology to develop innovative drug transport mechanisms and could lead to the evolution of nanomedicine [2,4,9]. Nanotechnology has provided a secure platform for designing and developing advanced drug delivery systems [10,11]. Till now, various drug delivery models ranging from several nanometers to several millimeters have been explored, including micelles, dendrimers, liposomes, nanoparticles, quantum dots, metal oxides, carbon nanotubes, and fullerenes [2,4,12–17]. To date, various novel nanomaterials, such as superparamagnetic iron oxide nanoparticles (SPIONs) [18], transition metal dichalcogenides (TMDs) [19], black phosphorus (BP) [20], and several organic and inorganic nanomaterials have been introduced as drug carriers, leading to the development of several DDSs (Table 1). Over the past few decades, carbon- based nanomaterials such as graphite, diamond, fullerenes, carbon nanotubes, nanowires, and nanoribbons have provided future perspectives for various applications [21–23]. Among these nanomaterials, graphene (G) has opened a new paradigm in the biomedical field owing to its remarkable properties [24–26].

The unique features of graphene and its derivatives have attracted interest on a global scale. They have been used to make a wide range of products, including sensors for the chemical and biochemical industries, capacitors for the storage of renewable energy. Its high conductance make it a suitable candidate for photovoltaic cells and liquid crystal displays in biodevices, and also impart an excessive capability for photothermal healing, bacterial inhibition, drug transport, and gene therapy [27,28]. Thousands of linked articles every year demonstrate the substantial growth in research efforts in this newly developing nanomaterial, as shown the graphs.The data collection of articles including graphene in the recent ten years is presented in Graph 1 and Graph 2 represented the number of the articles containing the search term “Graphene as a Nanocarrier.”

Several review papers have focused on the biomedical applications of graphene and GO. This review discusses recent developments and advances in the application of graphene and graphene derivatives as nanocarriers for drugs [29,30]. Therefore we provide a brief outline of all that is required for developing nanocarriers for drug delivery. The properties, synthesis, surface modification, functionalization, toxicity, biocompatibility, and chemical interactions of graphene and its derivatives have been highlighted as significant characteristics for their ability to serve as nanocarriers. Next, the most important examples of their delivery applications are summarized, along with their processes. Finally, we summarize the antiviral activity of graphene-based drug delivery systems, particularly against the human Covid-19 virus; pH-triggered doxorubicin graphene delivery system, as well as gene delivery and biotechnology of GO, its potential role as a biomarker sensor for cancer, and its toxicity.

2. Graphene and its derivatives

Graphene, a two-dimensional carbon monolayer with sp^2 hybridized carbons composed of tightly packed carbon atoms in a hexagonal honeycomb structure, was discovered in 2004 [52–54]. During this period the research on graphene has expanded tremendously, examining its many features and uses as electrical, optoelectronic, and photoconductive constituents [30,55]. Among the different graphene-related materials shown in Fig. 1. This material can be produced using numerous approaches, including mechanical shedding [54], oxidative shedding-reduction [56], arc discharge [56], liq.-phase shedding [56], and total organic synthesis [57].

2.1. General methods of graphene synthesis

Generally, graphene can be synthesized using two different routes: bottom-up and top-down, as shown in Fig. 3. In the top-down method, graphite is exfoliated or converted to graphene. In the bottom-up method, a self-deposition or self-assembling process of nanoparticles takes place. Geim et al. reported the isolation of graphene using the Scotch tape method [52]. Although, high-quality graphene flakes can be produced by mechanical exfoliation of graphite, this method is labor-intensive and only suitable for small-scale production. Controlling the number of graphene layers with large surface area with significant interface effects by using SiC substrate are main features of this approach [58–61]. Chemical vapour deposition (CVD) is the second procedure used to fabricate graphene. This procedure shows excellent outcome for producing graphene on a large scale. The following processes can be used to prepare graphene by chemically exfoliating graphite: chemical derivatization, intercalation, thermal expansion, application of surfactants, and oxidation-reduction [56,62]. This process eliminates the interlayer van der Waals forces. The use of powerful oxidants to prepare graphene oxide is the most typical method for chemically exfoliating graphite. B.C. Brodie was the first to prepare graphite oxide, which he subjected to a solution of potassium chlorate and nitric acid [54]. Later, Hummers and Offeman oxidized graphite using a solution of sulfuric acid, sodium nitrate, and potassium permanganate [52]. For instance, Marcano et al. discovered an improvement in the efficiency of oxidation when using a mixture of orthophosphoric and sulfuric acids and potassium permanganate [30].

3. Properties of graphene

The honeycomb sp^2-carbon structure of graphene is known for its elasticity, stability, electrical conductivity, and elevated lipophilicity due to the absence of oxygen groups and attaining a steady suspension in H_2O requires surface-active agents or extra stabilizing agents. In contrast, GO is the oxidized arrangement of graphene, produced mainly by the Hummers’ method, and contains various functional groups, such as carbonyl (C=O), epoxide (C-O-C) and carboxylic (-COOH), and others over the external area of GO, along with some sp^3 carbons that reduce the mechanical and electrical capabilities, but reduce it to very hydrophilic and water dispersible [52,63–66]. It is a hydrophilic derivative of graphene on the H_2O with a position of 30.7° and has a pair of aromatics (sp^2) and aliphatic (sp^3) fields that simplify the relationship in the surface area [57,59,67]. Furthermore, GO can be reduced by chemical/thermal reduction to partially regain its electrical conductivity and water dispersibility. The resulting rGO was examined as a middle structure since it holds properties of both graphene and GO [68]. The presence of few oxygen groups on rGO, make it less hydrophobic than graphene on other side these groups are not sufficient to match the higher basal reactivity of GO [69]. Additionally, this two-dimensional graphene can be exploited to make zero-dimensional structures, can be tuned into one-dimensional structures, or can be loaded toward three-dimensional structures [70–74]. The uniqueness of graphene has created hype in the scientific community owing to its following remarkable properties: a) purest form of carbon b) very large theoretical specific area (c) highest intrinsic mobility (d) extremely high mechanical strength (e) exceptionally high thermal conductivity (f) it has optical transmittance (g) light weight and thinnest known material in the universe (h) zero band gaps (i) outstanding elasticity. The main features of graphene and its derivatives are listed in Table 2 [62,75–80].

4. Surface modification and functionalization of graphene and its derivatives

Graphene, with its remarkable features, have attracted the interest of researchers in developing new graphene/graphene-based drug delivery systems (GDDS). However, graphene accumulates in biological fluids

Table 1
Nanomaterials used in drug delivery.

Nanomaterial	Size Range	Introduction	Applications	Limitations	Reference
Polymeric micelles	20–50 nm	Co-polymers having a water-hating part inside (core) and a water-loving part outside forms Polymeric micelles.	Both hydrophilic and hydrophobic block copolymers Tremendously small construction Rise water solvability of drugs	When injected intravenously into the blood, the micelles may disintegrate.	[31,32]
Dendrimers	01–10 nm	Highly branched, multiple-shaped polymers	Photodynamic treatment Boron neutron detention treatment Powerful anticancer compound	Certain dendrimer- constructed multi-role structures have revealed important cytotoxicity.	[33,34]
Polymeric nanoparticles	10–1000 nm	Solid colloidal particles in which the drug may be liquified, captured, encapsulated, or attached to a nanoparticle matrix.	Controlled release Therapy and imaging (theranostics), Specific targeting	Particle aggregation, polymer chemical instability, early deliver of the active material. Also, the liquid dosage forms are susceptible to microbial proliferation that requires the addition of preservatives.	[35,36]
Liposomes	90–150 nm	Made up of a lipid bilayer, the internal hollow portion can be filled with single or many medicament particles, mock cells about cell membrane	Outstanding biocompatibility Possible usage as a temperature- or pH-sensitive drug transporter.	Impart physical instability, due to their amphiphilic nature.	[37,38]
Polymeric drug conjugates	10 nm or less	Polymers are utilized as transporters for drugs, proteins, targeting moieties, and imaging agents in polymeric prodrugs/ macromolecular prodrugs.	Delivery of cytotoxic drugs Precise release Surge effectiveness, tolerability, and action of drugs	various dissimilar places of protein may be conjugated to the polymer particles, interfere occasionally with the dynamic recognition site, and retard the bioactivity of the protein.	[39,40]
Superparamagnetic iron oxide nanoparticles (SPIONs)	10–100 nm	Surface characteristics of nanoparticles, such as superparamagnetic iron oxide nanoparticles (SPIONs) with biocompatible polymers, and controlling their size within the desirable range can yield powerful targeted delivery vehicles	Effective in the identification of lymph node metastases, useful in treatment of prostate, breast and colon cancer	Low bioavailability and burst release	[20]
Transition metal dichalcogenides (TMDs)	0.6–0.7 nm	2D TMD nanosheets can directly interact with biomolecules resulting in their surface modification or decoration	Used for detecting the target molecules such as nucleic acids and proteins	Low Efficiency and costly	[21]
Black phosphorus (BP)	338–365 nm	2D Nanosheets can directly interact with plasma protein corona from blood	Used for identification of plasma corona	Loss of target capabilities	[22]
Silica nanoparticles	opening dimensions in the range of 250 nm	Silicate nanoparticles are enormously steady and less poisonous. Mesoporous silicate resources through fascinated by extensive care due to their accurately accommodated macroscopic arrangement, chemical functionality, and mesoporous structure.	Improved pharmacokinetic profile Enhanced bioavailability	Porous silica nanoparticles interrelating by the outward of the phospholipids of the RBC's membranes resultant in hemolysis. Also, induce immunotoxicity.	[41,42]
Gold nanoparticles	1–100 nm	Gold nanoparticles (AuNPs) are small gold particles and possess tunable and unique optical properties	Contrast agents Provide controlled target delivery	Non-specific targeting can stimulate the host's immune system. Unpredictable biodistribution behavior along with *in-vivo* instability and a shorter blood circulation time period.	[43,44]
Carbon nanotubes	width characteristically diverges in series 0.4–40 nm extent can differ from 0.14 nm to 55.5 cm	Carbon nanotubes (CNTs) are sp^2nanocarbon materials with tubular structures composed of rolled-up graphene sheets and exhibit remarkable properties.	Upsurge drug solubility and steadiness Target drug transport Combination therapy	Biocompatibility issues, cell-damaging effects, ability to collect in organs, creating oxidative stress and damage to healthy cells. Because of their shape and hydrophobic surface, CNTs generally get agglomerated.	[45,46]
Fullerenes	30-3000 carbon atoms. C60 with a diameter of 0.7 nm.	Carbon-belonged resources are utilized aimed at their basic capability to perform as anti-oxi.	Basic capability to act as an antioxidant.	Because of their strong binding to plasma proteins, they accumulate mostly in the liver.	[47,48]
Quantum dots	2–10 nm	These are the nanoparticles having distinct optical and electrical features, such as intense and	Luminescent effect Enhanced efficiency and	High in vivo toxicity, incomplete elimination, nonspecific binding with the organic molecule.	[,49]

(*continued on next page*)

Table 1 (*continued*)

Nanomaterial	Size Range	Introduction	Applications	Limitations	Reference
		brilliant fluorescence and shows adjustable optical features.	bioavailability Reduced side effects		
Magnetic nanoparticles	1–100 nm	Are nanoparticles type which will be simply traced, operated and aimed via outside electro-magnetic field and are created with elements iron, cobalt, nickel and their oxides.	Magnetic targeted delivery No toxic effects or incompatibility	Non-specific toxicity,	[50,51]

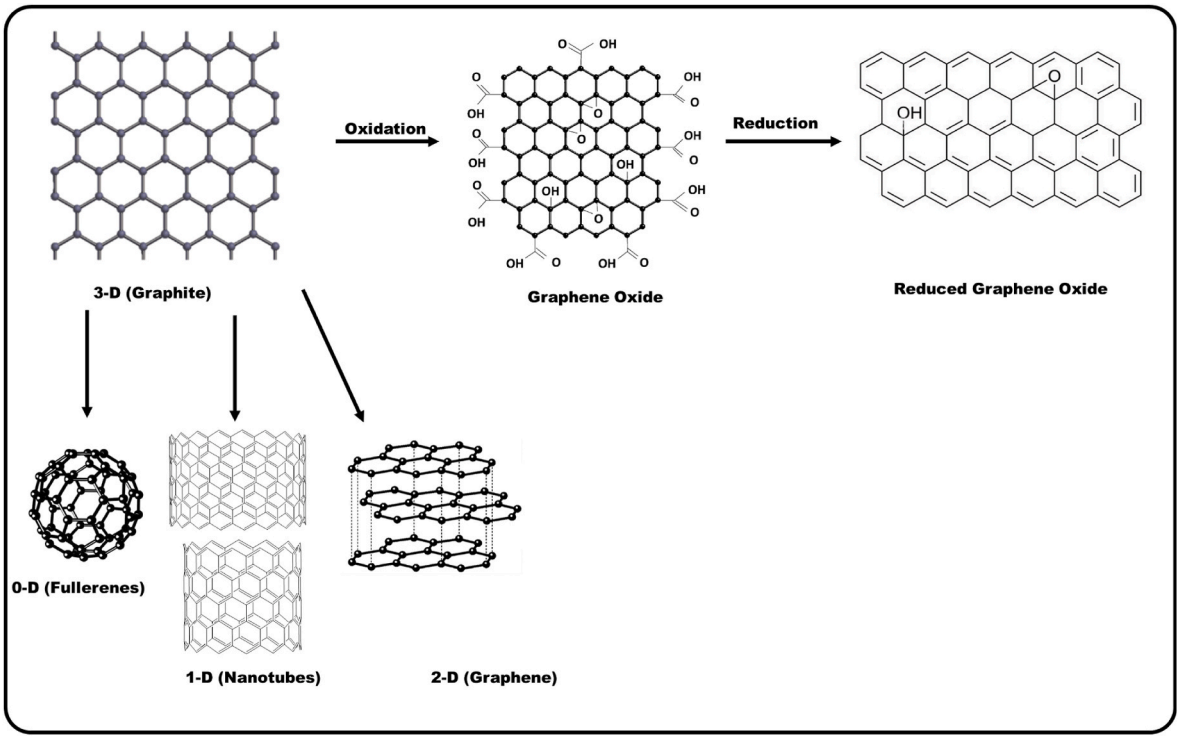


Fig. 1. Schematic representation of Graphene-based materials [29].

Table 2
Characteristics of graphene & its derivatives.

	Properties						
Material	Mechanical strength i.e; Yung's modulus (Gpa)	Fracture strength (Gpa)	Optical transmittance (%)	Charge carrier concentration (cm^{-2})	Room temperature mobility ($cm^2\ V^{-1}$)	Thermal conductivity (W/mk)	Electrical conductivity (S/cm)
Graphene	1000	130	97.70	1.4×10^{13}	I5-200,000	−5000	10^4
Graphene oxide	220	120	NA	NA	N/A	2000	10^4
Reduced graphene oxide	NA	NA	60–90	NA	N/A	0.14–087	200-35,000

N/A: Not available.

and causes cell death, and hence shows below-par bio solubility and biocompatibility [80]. To overcome these limitations, numerous external modifications have been made to improve water compatibility and biocompatibility [81]. Several studies have demonstrated that functionalization improves dispersibility, biocompatibility, reactivity, binding capacity, and detection ability [52]. More prominently, these changes show functionalized graphene owing to its excellent properties as both a carrier and adjuvant. The use of functionalized graphene is also an innovative drug delivery approach through activated release by means of peripheral stimuli, including pH, magnetic fields, or near-infrared radiation [49,51]. Graphene derivatives, the important graphene oxide (GO) can be altered to create super facial functionalization, either via covalent or non-covalent approaches [34]. The covalent method is usually achieved via reaction with oxygen species of graphene's unsaturated structure by several different methods, including nucleophilic substitution, electrophilic addition, condensation and addition. On the other hand, the non-covalent procedures cover Van der Waals forces and electrostatic binding without disturbing graphene's normal construction and this approach seems to be more convenient to handle, and can be attained through polymer covering, adsorption of surfactants or small particles and reactions with porphyrins or biomolecules such as DNA and peptides (Fig. 2). The GO can be improved

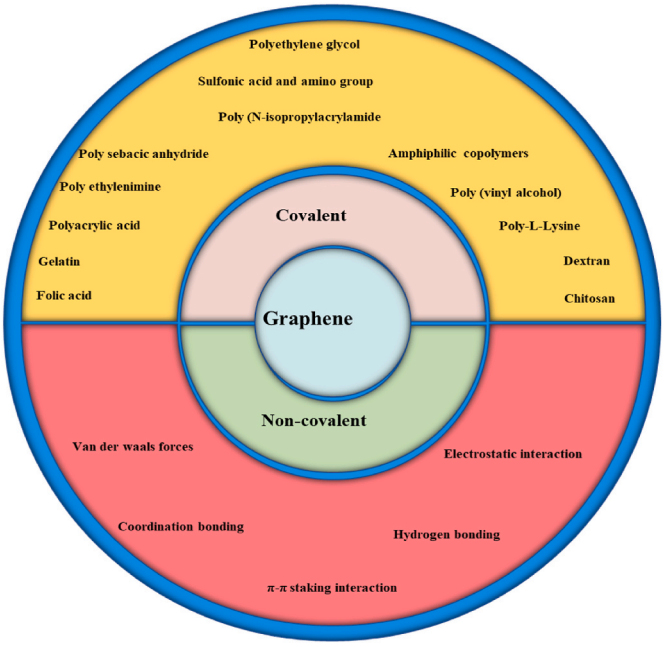


Fig. 2. Mechanism of covalent & non-covalent functionalized graphene & graphene oxide utilized for medicine transfer [86,87].

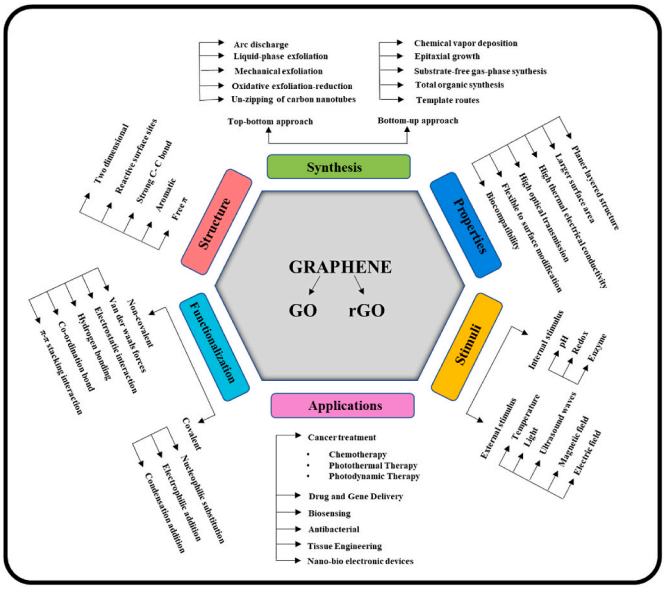


Fig. 3. Schematic representation of synthesis, stimuli, structure, applications, functionalization and effects of graphene and related materials [85–93].

by altering its outer surface to develop several carbon-based complexes using chitosan, citric acid, protamine sulphate/sodium alginate etc [82,83]. This change is feasibly attained through the chemical precipitation of functional groups; for example, a unique technique for establishing carboxylic acid on GO to build graphene oxide carboxylic acid (GO-COOH). GO-COOH can be utilized in addition to numerous biological dynamic sets such as myoglobin and protein control and it representes the diverse methods for functionalization of GO for tumor treatment [84,85].

The modification of graphene offers many advantages because the functionalization of chemotherapeutic drugs with graphene derivatives helps in structural changes, thereby avoiding effortless elimination, enhancing bio-distribution, refining extravasation volume, and prolonging the vascular flow period, providing an extra definite method of drug transport and creating a chemosensitizer. The use of GO in drug transport applications is shown in Fig. 3.

In recent years, various transporter have been synthesized using graphene as a building component [94–96] to design effective drug delivery platforms for drugs, genes, and biomolecules because of the appropriate extended surface area, biocompatibility, and lenience of surface functionalization offered by graphene and its derivatives [55,97,98]. Furthermore, drugs such as photosensitizers, genes, anticancer drugs, and proteins are equally effective in the analysis and treatment of diseases when fused with graphene-based materials [99].

5. Graphene-based drug delivery systems

5.1. Distribution of drugs via nano-structured based systems

The distribution of drugs via nanostructured systems for drug delivery has several advantages, such as the protection of drugs due to metabolism, enhancing the effectiveness of therapeutic agents, decreasing side effects on normal tissues, making medicinal agents more selective to a target site, and reducing dose frequency [8,100,101]. The rise of graphene-containing nano transporters has not resulted in the successful transport of mutually small particles and bulky biomolecules; also made the distribution of various agents possible. The very large surface area of the material, with every atom exposed on its surface, allows for ultrahigh medication and gene loading efficiency. These properties make graphene an ideal candidate for drug and biomolecular transport. It has achieved enormous success in drug delivery owing to its double exposed surface for conjugation, electrical conductivity, and ability to create plasma and fluorescence [102,103]. To date, researchers have used graphene and its derivatives to design several selected stimuli-responsive drug transport systems either via outer impulse, inner incitation, or multiple stimulus-response drug transport approaches with more bioactivity and improved temporal and spatial control at lower doses of medicaments, with less toxicity and adverse effects [104–106]. A multifunctional graphene-based nanocarrier for biomedical applications is shown in Fig. 4. Liu and his coworkers in 2008 first time investigated graphene for biological purpose and discovered GO as a novel drug nanocarrier using polyethylene glycol/GO for filling anticancer drugs through noncovalent bonding [103]. It has ignited the interest of researchers to explore graphene and its analogs for a wide range of biomedical uses, together with drug and gene transfer and biocompatible scaffolds for cell growth. As drug carriers, graphene sheets are in the top most consideration because equal sides of a single sheet can be designed for drug binding [107,108]. Further due to its nontoxicity and biocompatibility, GO has been widely employed in drug delivery applications among carbon-based polymers because of its

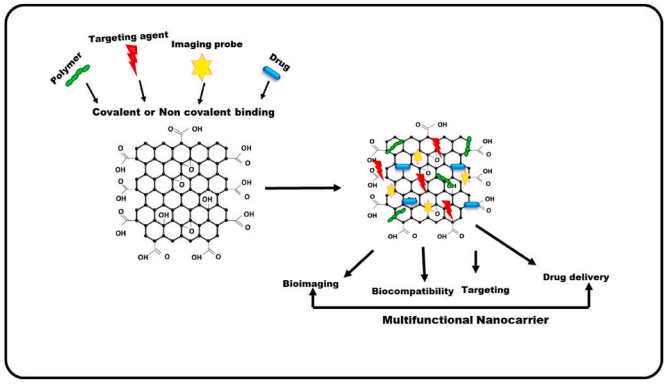


Fig. 4. Diagram depicting the multifunctional uses of graphene and GO nanocarriers, which are made up of various drugs, receptors (antibodies) aimed at cell target [13,116].

nontoxicity and biocompatibility. Many anticancer drugs, such as doxorubicin [109], sumatriptan succinate [110], methotrexate [111], quercetin [112], gefitinib [113], proanthocyanidins [114], cisplatin/DOX [115], 5-fluorouracil/Curcumin [116], camptothecin [117], and cytarabine [118], have the potential to be delivered via GO and GO-based nanocomposites.

Furthermore, the reactive functional groups on its surface, such as carboxyl and hydroxyl, permit conjugation with various desired groups results in a great augmentation of the multi-functional GO for various biological and clinical medical imaging uses [118–120]. However, natural polymers containing graphene not only promote biocompatibility but also aid in reducing harmful consequences. Gelatin acts as a functional group in DOX-deposited graphene nanosheets [121]. Because gelatin-graphene has a wide external part and more π-π relations, the process increases the medicament's packing capability. Many years ago, the gelatin–graphene–DOX complex demonstrated strong harmfulness toward MCF-7 cells, which might activate the approachable nanocarrier scheme for precise DOX-targeted drug transfer into the cytosol [122]. Subsequently, PEG-modified nano-GO (NGO) sheets were loaded with SN38, a camptothecin (CPT) analog, as an antitumor drug. The NGO–PEG–SN38 complex exhibited adequate H_2O miscibility while retaining SN38's significant in-vitro cytotoxicity. In addition, its strong cytotoxic effect was many times greater than that of CPT in HCT116 cells [122,123]. DOX was placed onto the PEG–NGO conjugate via non-covalent - stacking. Similarly, when the drug was released from the GO surface, GO has become pH-dependent. Consequently, the acquired pH-sensitive drug distribution was demonstrated using an additional GO-based drug delivery system [121]. In another aproach, the two antitumor drugs were filled with folic acid in the sense of π-π stacking in a regulated activity to find numerous pharmacological treatments for cancer therapy (DOX and CPT) [124,125]. Through the presence of folic acid receptors, the addition of GO by means of a folic acid ligand in the drug-loading approach demonstrated accurate directing action and comparatively greater cell toxicity than MCF-7 cells in human breast tumors [126]. Hence, graphene-based materials have proven to be an excellent approach to develop multifunctional nanocarriers. The delivery of various types of drugs using graphene-based materials is summarized in Table 3. Its demonstrated the way in which near-infrared (NIR) laser irradiation can be used in conjunction with GO nanocomposites to facilitate targeted drug administration and in vivo photodynamic treatment, as shown in Fig. 5.

Several hypothesized pathways of cytotoxicity caused by GOs are shown in Fig. 6. GOs enter cells through a variety of mechanisms that trigger the production of ROS, increase in LDH, and release of Ca^{+2}. Damage to cell membranes, inflammation, DNA damage, mitochondrial abnormalities, apoptosis, and necrosis are all the outcomes of GOs exposure [169].

5.2. pH triggered doxorubicin graphene delivery system

To transport and release DOX as a pH-dependent charge-reversal DDS, a nanocomposite of PEG-modified with 2, 3-dimethyl maleic anhydride (DA)-PEG-GO was synthesized [171]. It was found that, at a pH of 6.8, the nanocomposite charge switched to positive, causing an increase in PEG-GO-DA absorption by MCF-7 cells. However, at this pH, PEG-GO-DA/Dox was more effective in killing cells. PEG-GO-DA/DOX in conjunction with an 808 nm NIR laser showed greater efficacy in killing cancer cells by using the nanostructures' high NIR absorbance [171]. To produce a synergistic anticancer effect, a new receptor-mediated GO nano platform was functionalized with targeting and activating drugs, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and doxorubicin (DOX) [171]. As shown in Fig. 7, the nano platform accumulated at the tumor site, and after binding TRAIL to the appropriate receptors, they surrounded the cells. After the peptide linker and apoptosis trigger factor are cleaved by Furin, TRAIL induces death via caspase-mediated apoptosis. Finally, DOX-containing GOs are taken up into the cytoplasm and drug release begins in the acidic environment of endosomes [172,173].

People are seeking more effective treatment options because of the inadequate therapeutic effects and limitations of chemotherapy; therefore, research on drug delivery systems has been growing. However, the majority of this research largely concentrated on therapeutic benefits and attention to investigate novel drug-loading strategies and enhancing efficacy. Thus, unique fluorescence resonance energy transfer (FRET) systems have also been developed, and in addition highly luminous carbon quantum dots (CQDs) based nanosystems were synthesized [174]. In addition, a unique FGO-ADH-HA-Fe_3O_4 nanocomposite with a well-defined structure and excellent solubility in multiple media was also developed. It has outstanding turn-off fluorescence features for visual drug loading, special magnetism, and great photothermal efficiency for photothermal therapy (PTT) and hyaluronic acid dual-targeting against cancer cells [175]. Multifunctional nanosized fluorinated graphene oxide (FGO) demonstrated by researchers has also proved a revolutionary nanocarrier for precise and controllable delivery of single or combination anticancer drugs [176].

5.3. The effectiveness of graphene-based antiviral compounds, especially against the human Covid-19

Owing to their unique molecular architecture, CQDs can be modified using a wide range of functional groups to provide potent antiviral effects. For instant, the boric acid-functionalized CQDs exhibited antiviral efficacy against HCoV-229E. Here, two mechanisms were identified as responsible for the antiviral activities:1) the attachment of CQDs (with an average diameter of approximately 7 nm) to the S protein of viruses, thereby preventing infectious interactions between host cells and viruses, and 2) the ability of CQDs to inhibit RNA genomic replication. Barras et al. observed similar results after studying the anti-HSV-1 effects of carbon nanodots functionalized with 4-aminophenyl boronic acid hydrochloride. The antiviral properties of CQDs are shown in Fig. 8) [177–179].

5.4. Delivery of biomacromolecules

Graphene-based materials can not only transport tiny particles but also proteins and peptides. In a previous study, amine-containing GO was loaded using protein therapies, and it was discovered that the medicines were protected from enzymatic hydrolysis throughout the delivery procedure [180]. In addition to proteins and peptides, graphene can also transport nucleic acids [181]. This is partly because of the interactions between graphene and nucleobases. Varghese et al. confirmed such interactions using isothermal titration calorimetry and discovered that the binding power between graphene and guanine was the strong [182]. Because graphene and its byproducts can prevent the enzymatic destruction of DNA [183,184], they have also been shown to serve as non-viral transporters [177]. Graphene-based transporters are frequently functionalized with polycations to improve nucleic acid loading efficiency. PEI is a commonly used polycation [185] linked to related charged nucleic acids [186,187], and also provide active groups for additional functionalization to improve transfection effectiveness and tissue-targeting capability. A previous study of functionalized GO with PEI as a gene transporter discovered that PEI moieties allow the transporter to combine with nucleic acids and improve complex adherence to the plasma membrane for improved cellular uptake. PEI-functionalized graphene-based transporters have been widely used in gene therapy for various illnesses, including myocardial infarction, osteoporosis [188], and tumors [189]. Other agents such as chitosan, in addition to PEI, have been used to alter graphene-based resources for improved transfection[173,184,190–197]. The delivery of genes and biomolecules using graphene is shown in Table 4. Gene therapy is a potential treatment option for a variety of illnesses triggered by genetic abnormalities together with tumors. Compared with pure PEI, GO–PEI

Table 3
Delivery of various types of drugs using graphene based material

Category	Drug	Graphene-based composite/conjugate	Inference/highlights	Reference
Anticancer	Doxorubicin	CTX-GO/DOX	CTX-GO/DOX conjugate enhanced accretion of DOX inside glial cells and provided validation for emerging a glioma-specific drug transport system	[127]
		GC–GO–DOX	GC–GO–DOX continued steady below physical circumstances, and showed a pH-dependent drug release (tumor environment).	[128]
		ICG/DOX/GO-PPF68	Found optimum in vivo accumulation and superior therapeutic efficacy corresponding to MCF-7/ADR tumors and treatment of MDR cancer.	[126]
		TFGP*DOX	TFGP*DOX showed a controlled double target drug delivery, no harmfulness & improved depressive result on SMMC-7721 cells	[129]
		Dox-DNA-AuNP	Superior in -vivo antitumor properties of Dox-DNA-AuNP by obstructing cancer development related in the direction of unrestricted Dox in a creating SK-OV-3 xenograft mice model.	[130]
		NGO-PEG-RB- DOX	Rituxan (CD20 antibody) was used as a targeting agent to create pH-dependent tailored drug release	[129]
		PDM/DOX and PLM/DOX, SCM/DOX micelles	The comparative study showed that SCM would be a capable medicament distribution approach for cervical carcinoma	[131]
		PEG-BPEI-rGO-DOX	Endosome disruption caused by photothermal cytosolic DOX administration.	[132]
		DOX-GO–CHI–FA	In an acidic environment, pH-responsive drug delivery results in quicker DOX release.	[133]
		Gelatin-GS-DOX	The use of gelatin-made graphene for cellular imaging & DOX administration has been proposed.	[134]
		GO-Fe_3O_4	Drug delivery based on inorganic functionalization	[135]
		FeCo-GC-DOX	Photothermally boosted drug distribution using FeCo-GC nanocomposite, with improved distribution by more heat accomplished by NIR laser treatment.	[136]
		FA–NGO/CPT/DOX	For the first time, co-delivery of several medicines utilizing GO was demonstrated to have much greater lethal ness in MCF-7 cells when related to simply CPT or DOX.	[137]
		ADR-GO	The use of GO as a DOX carrier for drug resistance revocation in MCF-7/ADR cells resulted in excellent loading capability and pH-sensitive drug distribution.	[138]
	Docetaxel	Tf-PAH-(GO-DTX)	Improved efficacy of pH-dependent targeted drug delivery with high loading capacity	[139]
	Paclitaxel	GO-PEG-PTX	In a wide range of PTX concentrations and times, GO-PEG-PTX demonstrated exceptionally strong cytotoxicity to A549 and MCF-7 cells.	[140]
	Camptothecin	CPT-loaded GO-FA-CD	Significantly controlled drug delivery with high loading capacity for GO nanocarriers for CPT.	[141]
		PNIPAM-GS-CPT	Temperature-dependent drug delivery along with more CPT packing efficacy using PNIPAM.	
	SN38(CPT analog)	NGO-PEG-SN38	H_2O-immiscible antitumor drug delivery by more effective than CPT.	[142]
	Curcumin	DGO with curcumin and GQD-curcumin	GQDs demonstrated a great drug-packing capability of up to ~40,800 mg/g for a tumor therapeutic approach, and the study demonstrates that curcumin can suppress tumor development.	[143]
	SNX-2112	GO–CHI–HA/SNX-2112	pH-dependent drug release with reduced cytotoxicity against human bronchial NHBE cells (Epithelial)	[144]
	5FU	GN-CNT-Fe_3O_4	The drug was released in a pH-dependent manner, with minimal cell toxicity action on liver cells and effective utilization by HepG2 cells.	[14]
	Methotrexate	MTX-GO	Magnetic iron nanoparticles improved chemotherapeutic effectiveness through pH-dependent drug release and biocompatibility.	[111]
	Tamoxifen Citrate	Pyridinium bromide (PY + -Chol)-Graphene (GR)	Enhanced apoptosis of cancer cells	[145]
	Quercetin (QSR) Gefitinib (GEF)	Polyvinylpyrrolidone (PVP)-GO	Within a dose range, high biocompatibility and improved anticancer activity	[146]
	Ellagic acid (EA)	GONS-Pluronic F38(F38), GONS - Tween 80 (T80), GONS–Maltodextrin (MD)	Significant drug packing (For GO-T80, 1.22 g per 1 g)	[147]
Antibacterial	Metronidazole	MTD-Chi/GO beads	The medicine was released in a regulated, sustained, and prolonged manner by these biocompatible beads	[148]
	Gentamicin	MDG – gentamicin matrix	Demonstrated controlled release behavior of drug MDG nanosheets	[149]
		gentamicin-loaded graphene nanocomposite	Gentamicin-loaded graphene nanocomposite exhibited a bigger region of inhibition formed through the entire region of inhibition	[150]
Antibiotic	Tetracycline (TC)	Carboxymethyl cellulose (CMC)-Zn-Based Metal-Organic Framework (MOF-5)-GO	Effective protection against stomach pH and efficient oral drug administration	[151]
	Cephalexin	GO-PEG-CEF	GO-PEG-CEF is a promising nano-antibiotic system with long-term efficacy against S. aureus and B. cereus infections.	[152]

(*continued on next page*)

Table 3 (*continued*)

Category	Drug	Graphene-based composite/conjugate	Inference/highlights	Reference
Antiemetic	Ondansetron	Ondansetron loaded Pluronic® F127 stabilized reduced graphene oxide hydrogel (2% Carbopol 940 base)	A potential transdermal delivery method capable of maintaining & modifying drug release profiles with enhanced bioavailability	[153]
		rGO-Ondansetron	A flexible polyimide-based patch was created by dispersing (rGO-Ondansetron) nanosheets on top of Kapton. The patch's release approach was predicated on inducing a high temp. with a laser ray. The photothermally generated heat expansion modifies Ondansetron's bond for rGO, resulting in regulated Ondansetron release from the patch	[154]
Antimicrobial	Ciprofloxacin	CF-loaded GPH film	Highly stable, with additional drug-loading sites. The findings of the CF-loaded GPH film showed gradual drug release with no early burst impact	[155]
Antidiabetic	Metformin	GO + MH hydrogel	Significant sustained metformin release for therapeutic tests demonstrated the biocompatibility of GO even at 100 μg/mL dosage concentration.	[156]
	Nateglinide	NTG-loaded GO-CS nanocomposite.	Nateglinide dosing frequency and potential side effects were reduced by using GO-Chitosan nanocomposites as a sustained release carrier system.	[157]
	Insulin	Insulin-loaded PEGDMA-rGO hydrogels	Insulin hydrogel has latent attention intended for the treatment of victims with diabetes because of the simplicity of insulin loading and reloading, additionally the ability to adjust release kinetics by varying irradiation period and radiation capability	[158]
Antituberculosis	Ethambutol	ETB-GO	The proposed formulation displayed great biocompatibility and sustained drug release	[158]
	Linezolid	GO-LZD co-administration	The anti-mycobacterial capabilities of isoniazid (INH), amikacin (AMK), linezolid (LZD), and GO were tested against Mtb H37Rv. Co-administration of GO-LZD has been proposed as a potentially effective anti-TB therapy.	[159]
	Isoniazid	GO-Py-CH and GO-INH,	The functionalization of graphene oxide by isoniazid & pyrazine-2-carbohydrazide improved the anti-mycobacterial action of the corresponding medicines & broadened their antibacterial range to include additional microbial strains in both planktonic and biofilm development states.	[160]
	Rifampin (hydrophobic) and Isoniazid (hydrophilic)	RIF–ISN–GO complexes	The results revealed that Rifampin (a hydrophobic drug) loaded more into the NCs than Isoniazid (a hydrophilic drug), and ISN release is quicker than RIF because it takes less effort to separate from the surface, and ISN is detached from graphene plates in less time. The Antibiogram test demonstrates that the loaded system outperformed pure medicines in controlling the growth of all susceptible and one-drug-resistant Mycobacterium.	[161]
NSAIDs	Ibuprofen	IBU@BC/GO	IBU@BC/GO results pH-dependent controlled release.	[162]
		IBU and 5-FU	IBU & 5-FU filled on FGOCs showed precise release actions & continuing biocompatibility	[163]
	Buprenorphine, Hyaluronic Acid (HA) (Osteoarthritis)	Bp-P-rGO-1000-hydrogel	Bp-P-rGO-1000-hydrogel showed sustainable release of the Bp owed to solid p–p contacts among drug and GO and prolonged the local numbness meant for treating subjects having numerous seriousness of diseases (chronic pain) in osteoarthritis similarly a lubricating environment for cartilage healing was given by HA reinforced with GO, which also had a significant impact on the control of the microenvironment in the joint cavity.	[164]
	Ketamine	K–P-rGO-1-Gel	Ketamine-laced Pluronic® F127-decreased graphene oxide hydrogel resulted in constant ketamine release because of the exclusive π- π stacking collaboration among ketamine and reduced graphene oxide and may be utilized to decrease neuropathic discomfort for a prolonged period while avoiding the related side effects of I.V, nasal, & oral routes.	[165]
H_2 blocker	Famotidine	FMT-CHGO	It demonstrated sustained drug release for up to 12 h, which is longer than the market product (Complete release within 2 h).	[84]
Flavonoid	Quercetin	GO-PVP-QSR-GEF	The functionalization of GO with polymers such as PVP improved its solubility and biocompatibility, with two anticancer medicines, quercetin, and gefitinib, demonstrating better cytotoxicity to PA-1 ovarian cancer cells than the individual drugs placed onto the GO polymer composite.	[113]
Protein	Allicin	CS/PVA/GO/Alli	Continuous release of Alli from pH-responsive CS/PVA/GO/Alli nanofibrous membrane, confirms the prolonged and excellent antibacterial action of Staphylococcus aureus.	[166]
Bronchodilator	Tulobuterol	T-rGO-500	The skin irritation research revealed that the F127-reduced graphene oxide hydrogel had adequate mechanical characteristics for topical administration and was safe (rabbit model). Ex vivo release research showed that rGO may maintain tulobuterol release for 72 h because of a strong - interface between the drug & graphene oxide.	[167, 168]
Flavonoids	Proanthocyanimides	GO–CS–Ext.	The GO-CS nanocomposite improved the biocompatibility of PAs-rich Ext., establishing a novel platform for the prolonged release of phytodrugs	[114]

(*continued on next page*)

Table 3 (*continued*)

Category	Drug	Graphene-based composite/conjugate	Inference/highlights	Reference
Antimigraine	Sumatriptan succinate	CS/TPP/GO/SS.	With less drug leakage in the stomach, CS/TPP/GO beads can efficiently carry the medicine to the intestine. The nanocomposite's cytotoxicity and antibacterial characteristics were evaluated, and the findings showed that the CS/TPP/GO nanocomposite hydrogel beads were biocompatible.	[110]

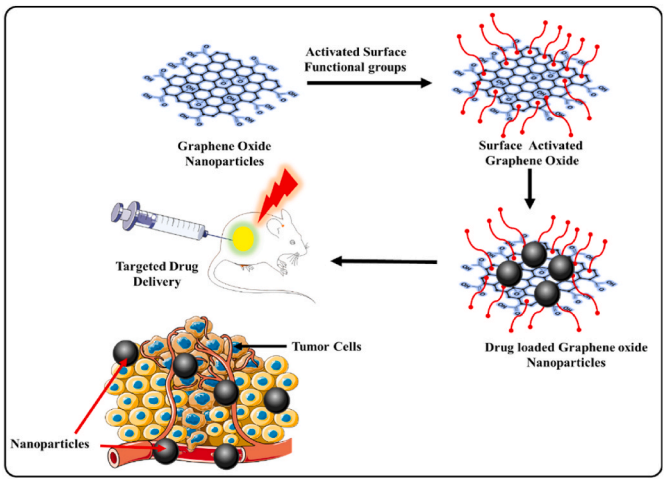


Fig. 5. Graphene oxide (GO) NPs had their surfaces changed, and then a drug and photosensitizer were loaded onto the modified GO-metal NPs [modified from Sharma et al., 2020 [169].

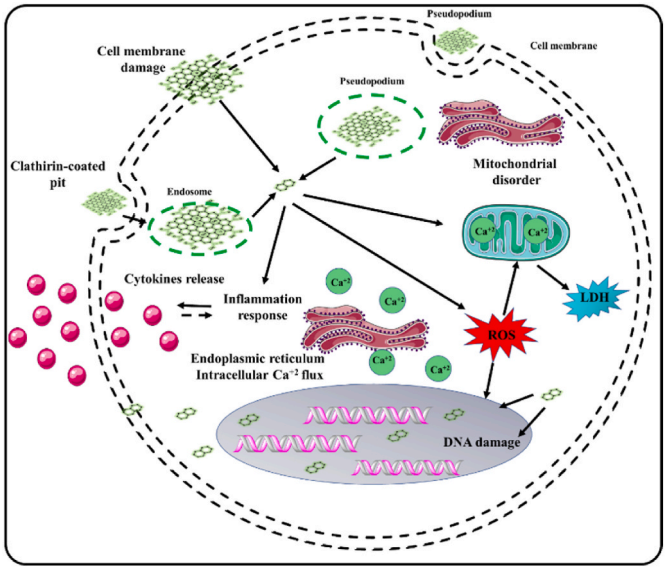


Fig. 6. The possible hypothesis of cytotoxicity of GOs modified from Ou et al. (2016) [170].

demonstrated less cell toxicity and greater transfection effectiveness at the appropriate mass ratio, making it an excellent gene vector [198, 200].

Furthermore, due to the inner physical features of their planar structures and large external zones, graphene and GO offer distinct advantages for loading various types of medicines and receptors [210, 211]. Owing to their outstanding capabilities, they have been widely exploited in the creation of a flexible drug distribution approach aimed in the combination treatments [212,213]. Additionally, graphene-based nanocarriers exhibit distinct relationships with DNA and RNA, making

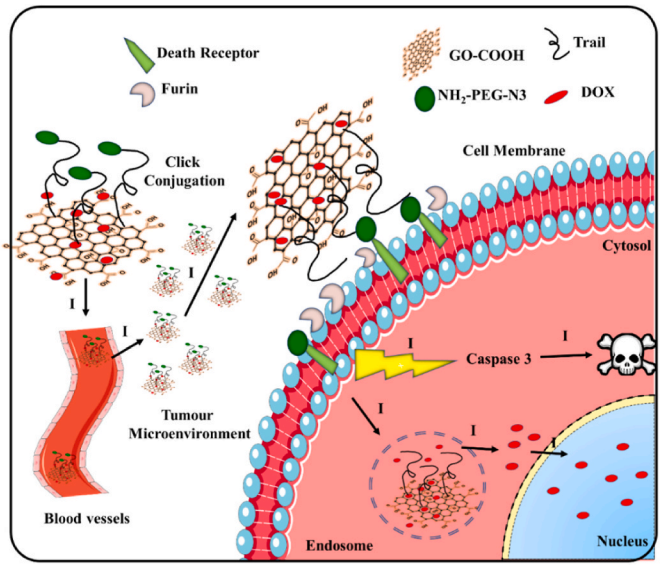


Fig. 7. Nanoplatform TRAIL/DOX-fGO scheme. TRAIL/DOX-main fGO's components (A) and its step-by-step action (B), from drug injection in the vessel to drug release in the cell nucleus; Modified based on work by Jiang et al. (2015) [172] and Hoseini-Ghahfarokhi et al. (2020) [173].

them appealing for DNA and RNA detection and distribution. Further, other carbon based carriers including GO/chitosan, GO-PEG, and GO/polyamidoamine can be utilized to carry plasmid DNA and siRNA [27,214–216].

5.5. Biotechnology applications

In medicine, graphene oxide (GO) has far-reaching effects. Owing to its high oxygen content, GO is hydrophilic and easily dissolves in water. The improved cell proliferation, drug loading, and antibacterial characteristics of the composites are also attributed to the presence of GO. As they are typically biocompatible and bioresorbable, feature a low immunological rejection risk, and may replicate the structure of the extracellular matrix. Electrospun composites offer significant promise for biomedical applications. This study provides a thorough account of electrospun composites incorporating GO for use in tissue engineering applications. Electrospun GO-containing materials have been investigated for potential use in drug and gene delivery, wound healing, and biomaterials/medical devices. GO's excellent biocompatibility and anionic exchange characteristics of GO make it as a promising material for pharmaceutical and biomedical applications [217] (Fig. 9).

5.6. Multipurpose nanocarriers for many therapies

The use of traditional therapies based on single therapeutic agents that can only reach a single target is insufficient because of the molecular complexity and defense systems of the disease. Combination therapy, defined as the simultaneous administration of two or more pharmacologically active medicines with various mechanisms of action, is acknowledged as a more effective method for treating diseases. Owing to their planar architectures and large surface areas, graphene and GO

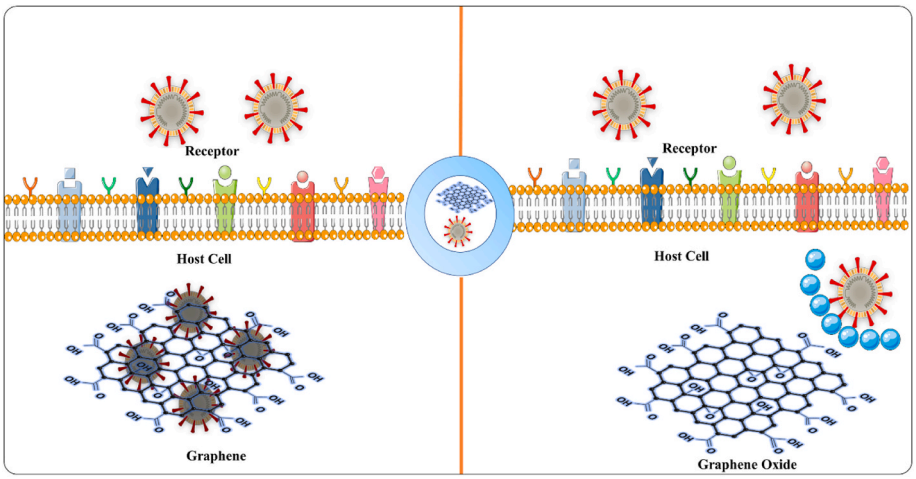


Fig. 8. For an illustration of the antiviral action of functionalized graphene QDs, Virus-related disorders are brought about by the S protein of the virus (HCoV-229E) interacting with the host cell receptor. The presence of ODs may reduce the effectiveness of such binding. This method can halt the replication of the viral genome modified by Seifi T et al. (2021) [177].

Table 4
Delivery of genes and biomolecules using graphene based materials

GO composite	Gene	Conclusion of the study	References
GO/PVA	VB-12	pH-sensitive polymer, suitable for cancer atmosphere	[199]
PAA-GO	BCNU	The multiuse transporter improved the drug's temperature steadiness and dramatically increased the half-life.	[200]
PPG	Adriamycin (ADR), miR-21	Dramatically increased ADR upregulation in MCF-7/ADR resistant cells, resulting in abundant cell toxicity than free ADR.	[201]
Ti-GO-BMP2	BMP2 protein	In in-vivo mice investigations, GO-coated Ti surfaces appear to be an excellent transporter for the therapeutic protein BMP2, resulting in increased variation of humanoid MSCS and strong new bone growth.	[202,203]
PEG-GO	Proteins ribonuclease A & protein kinase A	Protein distribution into cells lacking enzymatic degradation or loss of biological function.	[204]
PEI-Go	Gene delivery	Functionalization with GO decreases the harmful properties of PEI while increasing transfection efficacy.	[205,206]
PEI-GO	siRNA	MDA-MB-231 human breast tumor (in vitro). Effectiveness of siRNA delivery	[207]
PEI–GO	siRNA, DOX sequential delivery	Co-administering. of a gene and a drug in a sequential manner by more transfection efficacy and improved antitumor effectiveness.	[208]
PEG–GO	Proteins ribonuclease	A and protein kinase A Intracellular protein transfer without the enzymatic breakdown of biological function.	[209]

have a unique ability to load a variety of medicines and receptors [218–220]. Consequently, these materials have been used to create multifunctional drug delivery platforms for combination therapies. Fig. 10 schematically illustrates the concept of multifunctional graphene and GO-based drug carriers. This multipurpose drug delivery system

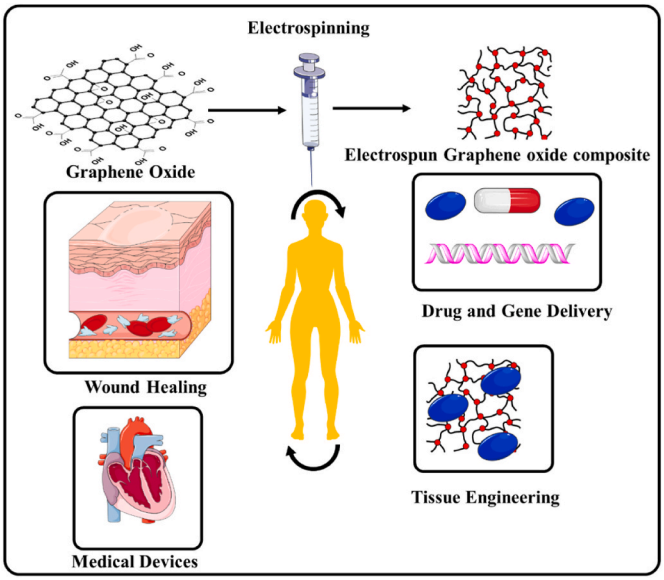


Fig. 9. Applications of GOs in Biotechnology (modified from Jamie. J. Grant et al. (2021) [217].

may provide a variety of therapeutic options, antibodies for cell targeting, and fluoroprobes for monitoring nanocarriers inside cells. Along with being used for biomedical imaging and cancer-specific drug administration, GO with and without a fluoroprobe can also be used as a possible cancer biomarker sensor [221].

5.7. GO in the treatment of POCD

Postoperative cognitive dysfunction (POCD) is a common complication of surgery and anesthesia that affects the central nervous system. This was marked by a decrease in cognitive performance. POCD is often seen in older people who often have trouble focusing, remembering, and learning after surgery. POCD is caused by a complex chain of events, including the buildup of amyloid beta (Aβ), hyperphosphorylation of tau protein, inflammation, synaptic dysfunction, and blocking of central cholinergic transmission. Therefore, the Aβ burden is one of the most studied topics in POCD. After surgery, cognitive problems in older mice can be resolved using drugs that prevent the buildup of Aβ in the brain. Inhaled isoflurane also changes how amyloid precursor protein (APP) is

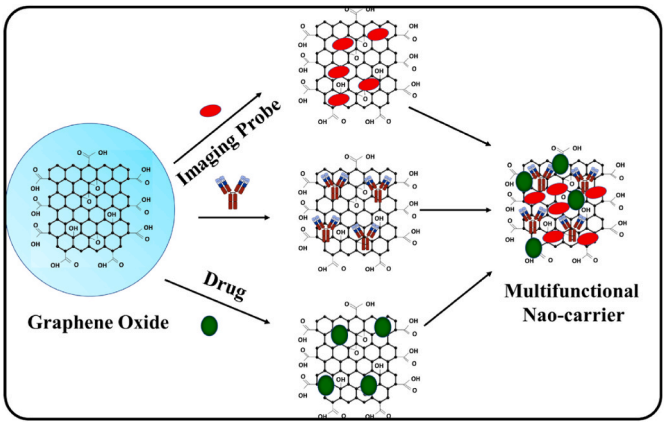
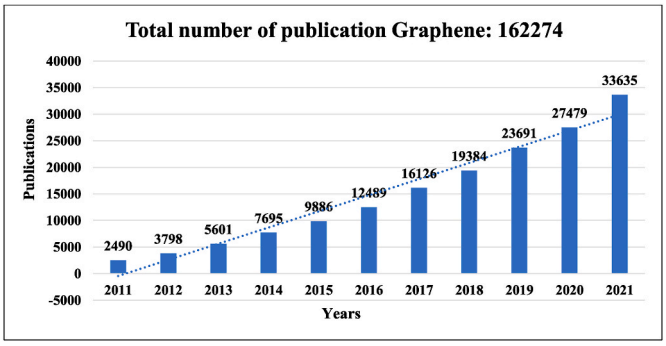
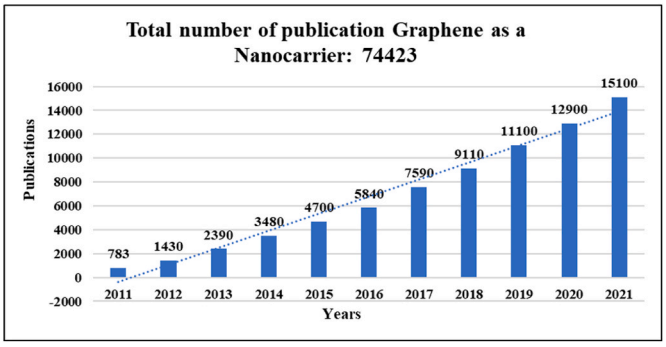


Fig. 10. Schematic of multifunctional graphene and GO nanocarriers illustrating the loading of several drugs, a receptor (antibody) for cell targeting, and a probe for imaging (tracking) the carrier inside the cell (Modified from Jingquan et al., 2013) [221].



Graph 1. Number of articles containing the search term "Graphene" in the defined time period during 2011–2021 (Science direct database).



Graph 2. Number of articles containing the search term "Graphene as a Nanocarrier" in the defined time period during 2011–2021 (Science direct database).

processed in human cell lines and causes them to produce more Aβ. These studies have shown that Aβ plays a key role in the development and pathology of POCD. Therefore, focusing on Aβ may be a good way to treat POCD. It was found that GO treatment reduced Aβ levels the most by reducing Aβ and making it break down faster. Surgery and anesthesia caused a sudden increase in the amount of Aβ in the hippocampal region and a loss of fear memory in mice that were 10 months old. However, the ntake of GO significantly decreased the amount of Aβ in the hippocampi and improved their ability to think. These results showed that GO could help POCD by preventing mice from receiving too much Aβ. This provided a evidence that GO-based nanomedicines, such as those for Parkinson's and Alzheimer's disease, could be used to treat diseases related to Aβ [222].

5.8. Toxicity and biocompatibility of graphene-based nanomaterials

Recent studies have focused on the toxicity and biocompatibility of graphene-based nanomaterials, both in vivo and in vitro. Two underlying factors have a significant impact on how different types of graphene interact with cell membranes: cell type and graphene morphology (lateral size, surface structure, functionalization, charge, impurities, aggregations, and chemical compositions). To further explain this, it was revealed that 10 nm thick graphene sheets may enter cells by penetrating them edge-first through their cell membranes and later accumulated in lungs epithelial cells and macrophages. However, GO typically exhibits low cytotoxicity at doses below 4 μg/mL. Additionally, rGO is less cytotoxic than GO, even at higher concentrations. This cytotoxicity may be the result of oxidative stress caused by the sharp edges of the nanoparticles, which damage the membranes. In accordance with earlier studies, the size of particles and the level of aggregation also affect GO cytotoxicity. Apoptosis, autophagy, necrosis, physical destruction, oxidative stress, DNA damage, and inflammatory response are the processes that underlies the toxicity of graphene-based nanomaterials [171,223]. In addition to toxicity, biocompatibility must be considered while exploring graphene-based nanomaterials for in vivo use or other biomedical applications. Studies have revealed that the dispersibility and solubility of graphene increase, as does its biocompatibility. GO sheets have many hydrophilic groups, such as carboxyl, hydroxyl, and epoxy groups, on their edges and basal planes, which significantly enhance their hydrophilicity. Additionally, hydrophilic agents applied to the surfaces of both graphene and GO have been claimed to significantly improve their biocompatibility [224]. Gelatin-modified graphene nanosheets were found to be biocompatible in the MCF-7 cell line and exhibited strong anticancer properties when loaded with DOX. It has been demonstrated that other modified types of GO, such as those with folic acid conjugation and sulfonic acid group modification, are biocompatible. Thus, the findings indicate that the toxicity, shape, and surface functionalization of graphene are inextricably linked with all factors, and the investigations are compared in accordance with biocompatibility. A comparison of functionalized and nonfunctionalized graphene-based nanomaterials revealed that the latter is far more hazardous [173,225–229].

6. Conclusion and future prospective

Nanomaterials can be used to deliver drugs in a controlled manner, and most of their recent work has focused on making nanomaterials based on graphene. Nanomaterials made of graphene have been shown to improve drug loading and release in a better way. Adding other nanoscale building blocks to graphene or GO, such as small molecules, nanoparticles, polymers, DNA, proteins, and peptides, could improve biomedical applications and drug delivery systems. Because graphene has a unique structure (2D, a single layer) and properties, its use in medicine will grow as it becomes easier and cheaper (high stability, strong conductivity, easy modification). In recent years, many studies have examined how graphene-based nanomaterials can be used to deliver drugs. However, some areas still require further research. The methods used to prepare monolayer graphene (GO and rGO) and the biomolecular changes that occur, such as those involving proteins, peptides, DNA, and other molecules, need to be improved. Monolayered graphene-based bio-nanohybrids show promise for applications in drug delivery, biosensing, and tissue engineering. The development of novel, perfectly compatible nanomaterials using graphene and its associated materials is a state-of-the-art tool that could pave the way for a revolutionary method for drug delivery and regenerative medicine. The core of every decision-making process continues to be weighing production

methods against cytotoxicity and performance, and graphene materials are becoming increasingly popular in cutting-edge medicine. Graphene's exceptional electrical properties and excellent tunability provide a foundation for expanding the material's use in biological context. These elements might increase their viability and open the door to a prosperous future for graphene-based materials. Graphene-based nanomaterials should be studied to determine whether they are safe for living things and whether they are harmful to cells over time. Even though, most research in these days focuses on obtaining medications for drugs, graphene-based nanomaterials can be used to diagnose and treat Parkinson's, Alzheimer's, and many other diseases, such as antibacterial, antibiotic, antiemetic, antimicrobial, antidiabetic, antituberculosis, NSAIDs, H2 blockers, bronchodilators, and antimigraine.

Declaration of competing interest

The authors declare no conflict of interest regarding this work.

Data availability

The authors are unable or have chosen not to specify which data has been used.

Acknowledgments

The authors are thankful to Prof. (Dr.) Sumeet Gupta, Director/ Principal, M. M. College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), for providing the necessary facilities.

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