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Graphene/carbohydrate polymer composites as emerging hybrid materials in tumor therapy and diagnosis

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ABSTRACT

Despite the introduction of various types of treatments for cancer control, cancer therapy faces several challenges such as aggressive behavior, heterogeneous characteristics, and the development of resistance. In contrast, the methods have depended on the creation and formulation of nanoparticles to impede tumor growth. Carbon nanoparticles have attracted considerable attention for cancer therapy, with graphene nanoparticles emerging as promising vehicles for delivering drugs and genes. Moreover, graphene composites can enhance immunotherapy, phototherapy, and combination therapies. Nonetheless, the biocompatibility and toxicity of graphene composites present difficulties. Consequently, this manuscript assesses the alteration of graphene nanocomposites using carbohydrate polymers. Altering graphene composites with carbohydrate polymers such as chitosan, hyaluronic acid, cellulose, and starch can enhance their efficacy in cancer treatment. Furthermore, graphene composites functionalized with carbohydrate polymers for tumor ablation induced by phototherapy. Graphene oxide and graphene quantum dots have been modified with carbohydrate polymers to enhance their therapeutic and diagnostic uses. These nanoparticles can transport gene therapy techniques like siRNA in the treatment of cancer. Despite the breakdown of these nanoparticles within the body, they maintain excellent biosafety and biocompatibility.

1. Introduction

Cancer is the top cause of death worldwide, impacting 19 million in 2020, with cases expected to double by 2035 [1,2]. Cancer develops from alterations in essential genes caused by genetic or environmental influences, resulting in invasive illness. As cancer rates increase, the demand for sophisticated detection and treatment technologies rises, with early detection techniques becoming more popular, such as imaging and blood tests [3]. Various methods, including surgery, chemotherapy, radiation therapy, hormone therapy, and immunotherapy, are employed to eliminate cancer [4]. Surgery and chemotherapy are often used together in cancer treatment [5], with chemotherapy showing considerable efficacy against illnesses such as leukemia, lung cancer, and ovarian cancer. However, chemotherapy drugs may lead to side effects such as hair loss, nausea, vomiting, and reduced red blood cell count, which could raise systemic toxicity levels. Studies indicate that combining chemotherapy, radiation, and surgery for cancer treatment is more effective than relying on any single

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approach individually [5,6].

AC and various members of the graphene family, such as GO, rGO, graphene, and graphene quantum dots, derived from carbon-based substances, are increasingly attracting attention in research due to their beneficial characteristics [7]. These traits include an extensive surface area, a porous structure, and active groups. However, AC's efficiency is often limited by its low adsorption capacity, inability to fully degrade or mineralize contaminants, lack of recyclability, delicate surface architecture, and restricted conductivity. Both GO and rGO, key elements of GC category, face challenges such as poor dispersion in water and a tendency to create larger agglomerates. This clustering can significantly reduce their accessible surface area, which impairs their efficiency in functions such as water treatment and diminishes the chances of their reuse [8]. Furthermore, graphene composites face notable challenges in fields like energy storage, catalysis, and electrochemical sensing due to their hydrophobic characteristics, leading to the aggregation of sheets. This results in issues related to the form of substrates, including curling, folding, and corrugation [9–11]. Graphene is made up of a single layer of carbon atoms organized in a honeycomb lattice, forming a two-dimensional substance. In this configuration, the carbon atoms, connected through sp2 hybridization, are tightly grouped [12,13]. Graphene has been extensively studied in fields such as biomedicine, sensors, catalysts, energy storage, and optoelectronics because of its exceptional electrical and optical characteristics, high mechanical strength, thermal conductivity, large surface area, and compatibility with biological systems. These unique characteristics have enabled its use in a variety of applications [14–18]. Additionally, the remarkable flexibility, electrical conductivity, and mechanical strength of graphene render it an ideal option for creating flexible electronic devices. These applications include electronic skins and adaptable energy storage systems [19–21]. CVD faces challenges like overlapping grain boundaries, pinholes, microcracks, and etching, hindering graphene's mechanical properties and limiting its effectiveness in various applications [22]. Numerous researchers have started incorporating graphene as a filler into different polymers to enhance their electrical, thermal, and mechanical characteristics, since polymer matrices typically exhibit insulation [23–26]. This is because graphene has exceptional qualities when compared to other materials. For instance, graphene has a superior surface area-to-volume ratio compared to carbon nanotubes, enhancing polymer matrix properties [24]. Graphene has been incorporated into numerous polymers over the past decade, including PVDF [27], PEMMA [28], PVDF-HFP [29], and PE [30]. Researchers have employed different fabrication methods such as melt blending, solution mixing, and in-situ polymerization to create graphene-infused polymer composites. These materials demonstrate excellent thermal and electrical conductivity, rendering them ideal for semiconductors and uses in electronics, energy storage, e-textiles, and heat sinks, rivaling metals and ceramics [31–35]. Different elements affect the physical and chemical characteristics of polymer composites formed with graphene. These elements include the type of graphene and its fundamental properties such as purity, size, and aspect ratio [29,36], as well as the degree of wrinkling and defects present in both the graphene and polymer composite [37], the connection between the polymer and graphene, and the arrangement of the graphene network within the polymer matrix [24]. Regarding the features and significant developments of graphene-based composites, their application in the medical sector has significantly increased. They have advanced cancer treatment through drug delivery [38,39], gene therapy [40,41], strengthening immunotherapy [42,43], providing cancer phototherapy [44–46] and improving cancer detection [47]. Therefore, this paper investigates the possibilities of graphene/carbohydrate polymer composites as innovative materials for cancer treatment and detection, emphasizing the synergistic integration of graphene's large surface area, unique physicochemical properties, and ease of functionalization with the biocompatibility and targeting capabilities of carbohydrate polymers like chitosan and hyaluronic acid. These composites address graphene's limitations, such as hydrophobicity, poor dispersion, and potential toxicity, by enhancing biocompatibility, stability, and water dispersibility, making them suitable for biomedical applications. Carbohydrate polymers enable targeted delivery through receptor-mediated mechanisms, improve controlled and pH-sensitive drug release in tumor microenvironments, and offer capabilities such as siRNA delivery, imaging, and combined chemo-photothermal therapy. This multifunctionality allows these hybrids to function as accurate medication and gene delivery systems, aiding in cancer phototherapy and diagnostic imaging while minimizing off-target effects and systemic toxicity. Incorporating carbohydrate polymers improves graphene's capabilities, leading to versatile, biocompatible nanocarriers and therapeutic devices that address current challenges in cancer, offering hopeful advancements for precision medicine.

2. Graphene composites: principles, properties and synthesis

Within the realm of carbon nanomaterials, GO and rGO rank as the leading two GBNMs [48–51]. Both GBNMs exhibit excellent biocompatibility and a variety of applications in biomedicine, due to their distinctive composition and structural characteristics [52]. Both GO and rGO have common features, as they consist of two-dimensional, single-atom-thick layers of carbon atoms structured in a honeycomb lattice, accompanied by a network of delocalized π electrons. Despite sharing similar traits, differences in structure between GO and rGO influence their unique properties. Graphene oxide generated via the Hummers and Offeman method [53] by oxidizing graphite in an acidic solution. Graphite is oxidized and mechanically treated to react with water molecules, leading to the separation of stacked sheets into graphene oxide. As a result, the structure of GO shifts from the honeycomb lattice of graphite to a mix of sp2 and sp3 hybridized carbon atoms, which incorporate different oxygen-containing functional groups such as hydroxyl, epoxy, and carboxyl groups [54]. rGO is formed by reducing the oxygen groups in GO and reestablishing the sp2 network to a form similar to graphene. Different reduction methods consist of chemical, thermal, hydrothermal, and electrochemical processes [55], with variations in carbon, oxygen levels, and defect characteristics depending on the particular technique used. rGO exhibits enhanced electrical conductivity relative to GO, rendering it particularly advantageous for developing electrochemical biosensors [50,56]. Nonetheless, the elevated hydrophobicity of rGO and its limited dispersion in water pose challenges, as the incorporation of molecules typically relies on non-covalent interactions like π–π stacking and electrostatic forces. This might result in desorption hazards in unexpected locations, requiring careful planning in drug delivery applications. In contrast, GO has a greater affinity for water, disperses more effectively in aqueous solutions, and can be altered with various biomolecules through covalent or noncovalent interactions, improving its efficiency as a drug delivery vehicle [57,58].

Graphene and its derivatives have been widely utilized in sensor production due to their unique physicochemical properties [59,60]. These nanomaterials are two-dimensional, measuring just a single atom in thickness at the nanoscale [61]. Graphene consists of a solitary layer of carbon atoms structured in a honeycomb configuration, with dimensions ranging from nanometers to centimeters [62]. Park and Ruoff [60] emphasize that graphene's sp2 hybridization allows for π–π conjugation, promoting effective electron transfer in electronic applications. For a material to be classified as graphene, it must consist of just a single layer of carbon atoms. When you pile several layers of carbon, the substance is referred to as multilayer graphene or graphite, based on the configuration and quantity of layers. Bonanni et al. [63] noted that the electrochemical characteristics of graphene are greatly affected by its layer count. Graphene films or foams, consisting of multilayer graphene, are often chosen for electrochemical applications. While single-layer graphene exhibits excellent conductivity, a slight reduction in conductivity can be observed when multiple layers are stacked [64]. As

a result, these materials offer greater adsorption and interaction with electrochemically active compounds, leading to improved electrochemical performance [65,66]. Multilayer graphene is more affordable and readily available than single-layer graphene, rendering it a viable option for electrochemical applications. Methods for synthesizing graphene comprise top-down and bottom-up techniques [64].

Graphene synthesis generally falls into two categories: the top-down approach and the bottom-up approach [67,68]. Various techniques employed for fabricating nanostructures consist of top-down, reducing materials to particles, and bottom-up, assembling atoms to create crystal layers. Every method possesses its unique benefits and drawbacks. In 2004, graphene was first produced by mechanically peeling graphite layers. This technique can yield high-quality graphene sheets in either monolayer or few-layer configurations [69–71]. While the process is lengthy and unsuitable for large-scale production, it also poses difficulties in controlling the amount and dimensions of layers [71–73]. On the other hand, chemical synthesis methods are performed at lower temperatures, making them more appropriate for producing graphene on various substrates at room temperature, particularly polymer ones [72,74]. Despite this advantage, the graphene produced through this method frequently exhibits variations and is not uniformly distributed across large areas [72].

3. Graphene composites in cancer therapy

A novel technique was utilized in the formation of nanocomposites derived from GO, which were evaluated for their efficacy in combating cancer. Cytotoxic effects were assessed on three cancer cell lines, focusing on cell cycle distribution and apoptosis analysis. GO-CS nanocomposites exhibited the strongest effect on breast cancer cells, with a specific focus on MCF-7. GO-EDTA halted the cell cycle in G0/G1 [75]. The study explores PG and h-BN sheets for delivering anti-cancer drugs cytarabine and clofarabine, finding PG exhibits superior reactivity and adsorption, highlighting its potential as an effective drug delivery vehicle [76]. UGO modified with poly(dopamine) has been used to develop a nanoplatform for delivering drugs aimed at cancer treatment through a combination of chemotherapy and PTT [77]. The UGO (UGP) nanoplatform demonstrates biocompatibility, substantial photothermal efficiency, and remarkable DOX loading capacity, facilitating targeted breast cancer therapy through NIR laser. Furthermore, scientists created a no-wash fluorescent aptasensor for the sensitive detection of mCRC LoVo cells, employing FRET between GO and the 5-carboxyfluorescein (FAM)-tagged W3 aptamer. This W3 aptasensor successfully detects mCRC cell lines, distinguishing target cells at a 5 % concentration, underscoring its promise for early mCRC identification in human blood [78]. This study integrated two novel phosphoramides, L1 and L2, altered GO, and analyzed their toxicity on breast cancer cells [79]. The research found that GO-L1 and GO-L2 exhibited potent inhibitory effects, with GO-L2 displaying the greatest cytotoxicity. Quantum calculations enhanced the structures, and docking tests demonstrated how the compounds attach to DNA polymerase IIα. Connecting phosphoramide compounds to GO enhanced their anti-cancer efficacy, especially in photothermal therapy using DOX. GO nanoparticles have the ability to transport anti-cancer medications and genetic instruments to boost cytotoxic effects and diminish drug resistance. Surface modifications and hybridization with nanocarriers facilitate targeted delivery of DOX-loaded GO nanomaterials [80]. Studies show that gold nanoparticles and graphene oxide can enhance macrophage phagocytosis, effectively eliminating cancer cells in experiments and living subjects, offering a promising strategy for cancer cell regulation through the granzyme-perforin pathway [81]. Difficulties in applying siRNA technology for targeted cancer gene therapy involve gene transfection, stability in the bloodstream, and monitoring delivery. Graphene GQDs have emerged as a novel approach for accurate drug delivery and monitoring fluorescence imagery [82]. This study utilizes GQDs loaded with siRNA to successfully transport siRNA into HeLa cells, indicating potential for the secure delivery of siRNA and genes. The study further confirms the treatment efficacy of the GQD/siRNA complex. A novel protein fusion of TRAIL-S-layer (S-TRAIL) together with GQDs has been developed to improve its efficacy in cancer treatment [83]. The research revealed that a nanohybrid system incorporating graphene and carbon nanodiscs successfully triggered apoptosis in TRAIL-resistant cancer cells. This illustrates the ability of nanotechnology to enhance the therapeutic effectiveness of TRAIL and presents a hopeful treatment alternative for cancer [84]. The oxidation enhances the hydrophilicity and oxygen functionalities of these materials, rendering them ideal for drug delivery. In tests conducted outside of a living organism, it was discovered that quercetin negatively affects cancer cells, with GO-Quercetin causing cell cycle arrest and oxCNDs-Quercetin resulting in G2/M arrest. The binding of quercetin to these compounds showcases promising potential for targeted cancer therapy. Nanotechnology has improved the safety and efficacy of cancer therapies, as graphene nanoplatforms offer customizable options for integrating bioactive materials. A study investigated the impact of GCD, HEp-2 reaction to DOX, and cancer-related intracellular pathways on cancer-associated pathways. Results showed that both DOX and GCD@DOX activated the p53 and p21 pathways, leading to a cessation of the cell cycle. GCD@DOX is a biocompatible drug delivery system that addresses chemoresistance and minimizes the toxicity of doxorubicin [85]. The study explains the preparation of biocompatible graphene nanocarriers, which were coated with IONPs, utilizing MPC and PEGMA [86]. Nanocarriers were evaluated for drug delivery, showing minimal toxicity on their own but considerable toxicity and DNA harm when used alongside DOX. The research investigated (Ag)1-x(GNPs)x nanocomposites, demonstrating significant antifungal and cytotoxic activities against *Alternaria alternata*, U87 cancer cells, and Congo red dye, while validating the photochemical characteristics of Ag-graphene nanocomposites [87]. CRC is an exceptional global cancer, accounting for 10 % of newly identified cases. Present imaging techniques and chemotherapy have constraints. A novel nanotheranostic agent was created to accurately diagnose and treat colorectal cancer. Graphene oxide quantum dots were labeled with a peptide (GILGFVFTL) that has a strong affinity for PLAC-1. The QD-P showed improved targeting and specific internalization in cells that express PLAC-1, resulting in greater cell destruction, reduced invasiveness, and lowered PLAC-1 levels [88]. A magnetic nanobiocomposite was created with modified graphene oxide and Fe3O4 nanoparticles for hyperthermia treatment. The composite showed stability in aqueous solutions and favorable chemical and structural attributes, rendering it apt for fluid hyperthermia therapy [89]. A research report describes a nanoplatform utilizing 2D carbon nanomaterial GO that converts into 3D colloidal spheres with mPEG-PLA. This platform incorporates Dox, demonstrating improved apoptosis, cell cycle inhibition, and photothermal effects, leading to greater reduction in tumor growth and lung metastasis compared to Dox by itself [90].

4. Carbohydrate polymer-modified graphene composites

4.1. Chitosan

4.1.1. Chitosan properties

Chitin, sourced from crustaceans and insects, is extracted using microbial proteases from various bacteria [91–93]. A heteropolymer composed of *N*-acetyl-D-glucosamine and D-glucosamine segments connected via β-(1–4) linkages [94]. Chitin's high biodegradability and biocompatibility limit its use in cancer drug delivery due to its crystalline structure, which reduces solubility and resists chemical changes [95]. Chitin has below 10 % deacetylation, molecular weight up to 2500 kDa, 5000–10,000 monomers [96]. Chitosan is a versatile carbohydrate formed from *N*-acetyl-β-(1–4)-D-glucosamine by removing acetyl groups from chitin [97,98]. The properties of chitosan, both chemical and biological, render it a potential candidate for drug delivery. As a bioadhesive polymer containing polycationic molecules, it rapidly bonds to

surfaces such as mucosal membranes. Extending the duration of action on mucous membranes enhances the efficacy of medications by prolonging their contact [99]. Due to its intricate characteristics, chitosan can enhance the distribution of polyanionic substances like DNA, SiRNA, small molecule medications, and anionic drugs [100]. Cyclodextrin and chitosan carry opposite electrical charges. When brought together, they form a specialized drug delivery system capable of efficiently transporting both hydrophilic and hydrophobic drugs. The cone-like structure of beta-cyclodextrin enables it to encapsulate lipophilic drugs within its hydrophobic cavity via hydrophobic interactions [101]. This leads to improved solubility, loading efficiency, and stability for lipid-soluble drugs. The relationship between the charge of chitosan and its ability to transport drugs underscores its role as a drug carrier that depends on pH levels [102]. Moreover, the positive charge of chitosan is responsible for its capacity to improve penetration. Chitosan's larger molecular size and high deacetylation rate boost epithelial permeability, facilitating the movement of polar drugs through epithelial membranes [103]. Both its compatibility with biological systems and levels of toxicity have undergone substantial enhancements. The material is a biodegradable polymer that can decompose into harmless molecules that the body can absorb [104].

4.1.2. Chitosan-functionalized graphene composites in cancer therapy

Breast cancer represents 23 % of cancer-related deaths in women, positioning it as the second primary cause of these fatalities [105]. The study emphasizes creating customized therapies with natural substances to address drug resistance and enhance the effectiveness of cancer treatment [106]. Curcumin, a phenolic substance found in turmeric, has various biological effects, including anti-inflammatory, anti-cancer, and anti-mutagen properties [107]. However, the therapeutic efficacy of curcumin is limited due to its hydrophobic properties, low solubility, and brief half-life [108]. CS-Fe3O4-RGO nanocomposites delivered Cur to suppress MCF-7 breast cancer cells effectively [109]. This was accomplished using a straightforward water-in-oil (W/O) emulsification technique. The average size distribution and surface charge of nanoemulsions were assessed using the DLS analyzer and zeta potential measurement. The SEM mapping verified a smooth and even surface on the NC, as shown by the EDX diagram. Fe3O4-RGOs exhibited superparamagnetic characteristics, confirmed by VSM measurements. The MTT assay showed significant toxicity of the NC against MCF-7 cancer cells. Flow cytometry analysis revealed apoptosis in the MCF-7 cells. Curcumin is released faster in acidic conditions via dialysis, while CEA is a valuable tumor marker for early liver metastasis detection Increased CEA levels might indicate different cancers or benign conditions. Tumor markers are generated by both normal and cancerous cells when cancer is present [110,111]. Several factors that may raise CEA levels include smoking, infections, inflammatory bowel disease, pancreatitis, liver cirrhosis, and specific benign tumors in the same organs, indicating possible malignancy if CEA levels are elevated [112]. Consequently, tracking CEA levels aids in identifying early cancer relapses after colorectal surgery [113]. Numerous research efforts have employed piezoelectric immunosensors, surface plasmon resonance [114], colorimetric assays [115], inductively coupled plasma-mass spectrometry [116], laser-induced fluorescence spectroscopy [117], electrochemiluminescent immunosensor [118], radioimmunoassay [119] and electrochemical immunoassays [120–123]. The study explores an antibody on a modified glassy carbon electrode for cancer monitoring targeting CEA. THi-CS-GO nanocomposites showed high sensitivity and specificity, with a detection limit of 0.8 pg/mL, and potential clinical application [124].

In recent decades, considerable attention has been directed towards the non-covalent alteration of graphene. This approach aims to enhance specific properties of graphene or mitigate its adverse effects [125,126]. A proposed method to modify graphene's surface without creating chemical bonds is the use of natural biodegradable polymers like polylactide, cyclodextrin, and chitosan, which may improve its dispersion and compatibility with biological systems [127]. Within this category of polymers, chitosan and its derivatives offer numerous advantages including biocompatibility, adhesion to mucosal surfaces, and responsiveness to pH levels [128–131]. The encouraging characteristics of chitosan-functionalized graphene warrant additional investigation into its structure and efficacy as a drug delivery mechanism. One instance is when Liu et al. [129] demonstrated that graphene coated with chitosan exhibits pH sensitivity and can disperse efficiently in both acidic and alkaline solutions. Furthermore, in studies carried out by other researchers [130,131], a graphene nanogel drug carrier modified with chitosan was developed, showcasing its temperature-sensitive properties and enhanced DOX loading capacity. The study explores the interaction between DOX and graphene modified with chitosan, revealing that adjusting the pH of the solution and the concentrations of the two substances allows for the control of loading and release. The grouping and dispersal of chitosan also influence the uptake and release of DOX molecules [132]. PEG is a polymer available in various molecular weights and functional groups. PEGylation improves the stability, solubility, and circulation half-life of nanomaterials in blood, thereby enhancing their pharmacokinetic profile [133]. Chitosan-pluronic F127 and magnetic reduced graphene oxide nanocomposites showed multifunctional properties. Their combination with α-mangosteen reduced breast cancer cell proliferation, suggesting potential for magnetically directed cancer therapies [134]. In 2010, Fan and associates employed a solution casting technique to produce graphene-chitosan composite films. Subsequently, they assessed the mechanical characteristics and biocompatibility of these films. Cell experiments indicated that L929 cells can attach and grow on the films, verifying their biocompatibility. Incorporating 0.1–0.3 % graphene into chitosan films led to an increase of over 200 % in the elastic modulus. The researchers suggested these composite films for scaffolds in tissue engineering according to their results [135]. This study investigates the physical properties of a thermosensitive and injectable hybrid chitosan hydrogel that incorporates graphene nanoparticles. The results confirmed that the thermosensitive chitosan-graphene hybrid hydrogel could act as a treatment option for breast cancer through the controlled release of methotrexate [136]. Nanocarriers are ideal for safe, efficient drug transport, especially in cancer therapy, due to their biocompatibility and efficacy. Research over the last fifty years on nanocrystals, liposomes, and micelles has spurred innovative alternatives in pharmaceuticals, enhancing patient care through better understanding of nanomaterial formation [137].

CRC is recognized globally as the third most common and deadly form of cancer [138]. It poses a major threat to human health [139] due to its elevated mortality rate and increasing prevalence. CRC is more prevalent in developed nations and more frequently impacts men [140]. Colorectal cancer begins in the cells of the colon, resulting in unusual growth. Individuals with conditions such as Crohn's disease or colitis face an increased risk. Elements such as smoking, alcohol consumption, unhealthy diets, genetics, epigenetics, and environmental factors can disturb oxidative balance, leading to CRC [141–143]. Antioxidant compounds can counteract free radicals, potentially lowering the likelihood of DNA mutations [144]. Treatment options for CRC include chemotherapy, immunotherapy, radiation therapy, and total surgical excision of the tumor [145,146]. Nonetheless, individuals often experience multiple side effects and face bleak outlooks following treatment [147]. The progression of CRC is divided into five stages, from stage 0 (the beginning) to stage IV (the most advanced), determined by factors like tumor invasion, metastasis, and lymph node involvement [148]. GTCEnc nanocomposites, composed of GO-TiO2-chitosan-escin, were created for a research study and evaluated through physical and biological methods to determine their capabilities in cancer therapy [149]. Diffraction, microscopy, and spectroscopy were employed to examine nanocomposites containing TiO2, GO, chitosan, and escin. The antibacterial characteristics of GTCEnc were investigated using multiple techniques such as MTT, EtBr/AO, DAPI, JC-1, Annexin-V/FITC, and cell cycle analysis to evaluate its effectiveness against COLO 205 cancer

cells. Results indicated an IC50 of 22.68 μg/mL for COLO 205 cells, exhibiting no toxicity to 293 T cells. Elevations in cytotoxicity, nuclear injury, apoptosis, and free radicals were noted in treated cells. The research additionally investigated CS, GO, and GO-CS against gram-positive and gram-negative bacteria, emphasizing chitosan's favorable zeta potential and its notable influence on HeLa cell growth and P53 protein elevation, suggesting its promise as an antibacterial and cancer therapeutic [150]. There is a theory that GO might function as a carrier for a substantial quantity of drugs to be attached to it. There has been a gradual but steady increase in research regarding GO, suggesting the possibility of its application as a drug carrier in the future [151–153]. A two-dimensional structural variant of monatomic carbon allotrope referred to as GO was discovered [154]. GO comprises various functional groups, including epoxy, hydroxyl, and carboxyl groups [155,156]. Graphene oxide features a high specific surface area and a structure that is connected with π. The loading of drugs onto GO can occur via interactions such as π–π stacking and van der Waals forces [157–160]. Numerous studies have concentrated on GO as a potential drug carrier possessing the aforementioned qualities. A study was carried out on a novel cancer therapy utilizing nanoparticles created from galactosylated chitosan, graphene oxide, and doxorubicin (GC-GO-DOX) [161]. In developing this drug delivery system, the medication was mixed with GC and incorporated onto a GO carrier. The results indicated that the highest drug loading capacity attained was 1.08 mg/mg (drug for polymer). The nanoparticles stayed stable under typical body conditions, but they released the drug in low pH environments, which are typical in tumors, and reacted to pH changes. In studies of cell uptake and cell proliferation, GC-GO-DOX nanoparticles showed higher cytotoxicity towards HepG2 and SMMC-7721 cells than CS-GO-DOX nanoparticles. The luminosity in cancer cells was significantly higher with GC-GO-DOX nanoparticles compared to CS-GO-DOX nanoparticles. Experiments carried out in living organisms demonstrated that GC-GO-DOX nanoparticles were more effective than CS-GO-DOX nanoparticles in suppressing tumor growth. Information on the nude mice's weight, tumor weight, and volume indicated that the tumor inhibition effect of GC-GO-DOX nanoparticles surpassed that of the control group and the blank group. The stable CHG-NPs exhibited a size of 213.6 nm and a zeta potential of +27.11 mV, effectively inhibiting ABTS/DPPH free radicals and demonstrating significant antioxidant activity [162]. Proof of reduced blood vessel number and dimension in CAM indicates angiogenesis suppression. Nanoparticles exhibited anti-angiogenic effects, shown by decreased VEGF and VEGFR gene expression in CAM vessels after higher CHG-NP doses. CHG-NPs displayed significant selective toxicity towards human A549 cancer cells, sparing normal HFF cells. 5-fluorouracil in chitosan-coated GCNCs was used for cancer treatment via microwave and 808-nm laser co-irradiation [163]. The application of chitosan on GCNCs reduced toxicity and improved cell cycle abnormalities in comparison to uncoated GCNCs. CS-GCNCs also showed lower 5Fu release rates, resulting in prolonged drug delivery. The speed of drug release was enhanced by integrating microwaves with an 808-nm laser. The ability of 5Fu to kill cancer, released from CS-GCNCs, was maintained by enhancing the production of caspase-3. The application of 5Fu-loaded nanoparticles alongside radiation led to a significant increase in cancer cell death and a decrease in tumor growth. The increased temperatures generated by GCNCs alongside co-irradiation, paired with the therapeutic effects of 5Fu, led to enhanced elimination of cells and tumors (Fig. 1).

Challenges in siRNA delivery include cytoplasm entry and reaching target cells due to negative charge [164]. It is crucial to mention that siRNA is commonly delivered through intravenous administration for different illnesses, bringing in extra elements for consideration. These factors consist of i) degradation by RNAse and ii) interaction with RISC.

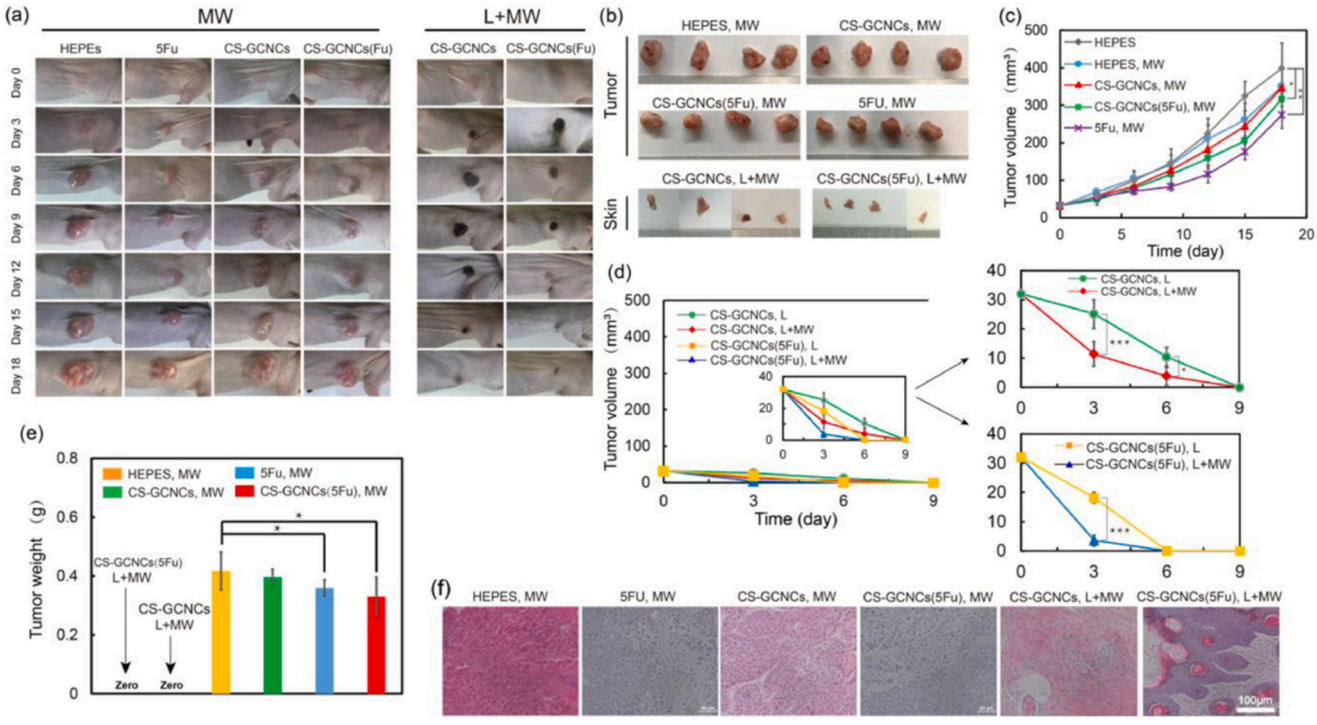

Fig. 1. The reduction of tumor development by CS-GCNCs, 5Fu, and CS-GCNCs(5Fu) occurred whether the tumor was subjected to laser irradiation, microwave irradiation, or a combination of laser and microwave irradiation. (a) Representative pictures of mice (all photographs are included in Figs. S6–S10). Please note that the images of the mice belonging to the "CS-GCNCs+L," "CS-GCNCs(5Fu) + L," and HEPEs groups. Morphologies of tumors or skin are also included. (c and d) The rates at which cancers grow. (e–f) cancers and skin (for the cancers that were not discovered) at the initial tumor location excised from mice 19 days after injection to represent the tumors that were not detected. These include (e) the weights of the tumors and (f) histological photographs of the skin or the tumors. *$P < 0.05$ was the threshold of significance that was observed. Lasers and microwaves are abbreviated as L and MW, respectively.
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Hence, the main goal of current studies is to discover an appropriate substance that can transport the siRNA to the desired location while also preventing its degradation during transportation. Even though recent research has demonstrated the promise of utilizing siRNA to treat breast cancer by targeting the epidermal growth factor receptor, the actual implementation of this method is still greatly restricted [165]. Chitosan nanoparticles with graphene oxide effectively delivered siRNA to osteosarcoma cells Saos-2 and MG-63, showing biocompatibility, efficacy, and minimal inflammation in acidic environments; clinical trials are underway [166]. Reducing the size of plasmid DNA using cationic polymers helps protect it from degradation and makes it easier for cells to take up the DNA [167]. Combining polymers with graphene provides numerous benefits, improving both the stability of the material and the effectiveness of gene delivery [168–170]. Adding graphene to the core of the gene delivery system increases its molecular weight, leading to a notable enhancement in transfection efficiency [171,172]. In this study, a graphene core was developed for gene delivery. Graphene oxide (GO) possesses oxygen-rich functional groups, allowing negative carboxyl groups to non-covalently bond with positively charged molecules [173]. The therapeutic gene, pDNA-TNF-α, was incorporated into a CS-CGO structure via electrostatic attraction [174]. To shield the vector from the mononuclear phagocyte system and prolong its circulation half-life, the pDNA-TNF-α-CS-CGO complex underwent additional passivation with 4,7,10-trioxa-1,13-tridecanediamine. In order to interact with folate receptors, which are more abundant in cancer cells, the inert carrier, made of PEG-pDNA-TNF-α-CS-CGO, was modified with folic acid-based carbon dots (C-dots). The successful modifications at every step of the C-dot-PEG-pDNA-TNF-α-CS-CGO formulation were confirmed by both the TEM images and zeta potential measurements. The final formulation showed anti-angiogenic effects in the chorioallantoic membrane following a 14-day incubation period. Research done on cancer cell lines using in vitro gene expression showed that the new system, C-dot-PEG-pDNA-TNF-α-CS-CGO, had much greater transfection effectiveness than pDNA-TNF-α by itself. Adsorption of DOX on both functionalized SWCNTs and graphene was effective. However, there existed a slight electrostatic and Van der Waals interaction between the drugs and carriers at cancerous tissues, offering significant advantages for cancer therapy. The presence of TMC polymer was necessary for promoting the delivery of DOX to acidic tissue. Moreover, the blood pH measurement showed that the PAX carried on the functionalized SWCNTs had the most evenly spread medication, while the DOX-graphene had the highest drug concentration in a specific area. Furthermore, the results from analyzing the MSD of PAX-graphene indicated that PAX was quickly absorbed and slowly released. To sum up, functionalized graphene-TMC-PAX is an intelligent drug system with responsive characteristics and controlled drug delivery, crucial for cancer treatment [175].

Chitosan-tripolyphosphate nanoparticles are recognized for intelligent drug delivery due to their simple manufacturing, cell compatibility, and versatility [176–179]. Nanoparticles possess great properties, yet their drug release often shows an initial burst of medication [180]. Studies suggest that the rapid release is mainly determined by the physical and chemical characteristics of the carrier and the drug's attraction to the carrier [181]. For example, physical loading of drugs into carriers can result in instability in the bloodstream, causing rapid release and a sudden spike in drug concentration. Prolonged release ensures a consistent and lasting level of drug concentration in the body [181–183]. pH-sensitive BSG/chitosan nanocomposites were created by utilizing electrostatic interactions between positively charged chitosan nanoparticles and negatively charged BSG [184]. These nanocomposites were employed to enclose DOX, a commonly used chemotherapy medication. Physicochemical assessments verified the effective integration of chitosan nanoparticles into BSG at different concentrations (0.5 %, 2 %, and 5 % by weight). The evaluation of DOX release over 28 days at pH 7.4 and 4.5 indicated that the quick release linked to chitosan nanoparticles was notably obstructed by the presence of BSG. Of the formulations tested, the 2 % BSG nanocomposite demonstrated the greatest effectiveness, realizing 84 % drug release over 28 days while maintaining a steady release pattern during the initial 24 h. Analysis of the release data suggested that BSG altered the release mechanism, facilitating a more regulated release in comparison to pure chitosan nanoparticles. Moreover, metabolic assays on SKBR-3 breast cancer cell spheroids verified that DOX released from the nanocomposites efficiently hindered cancer cell proliferation, especially in acidic environments [185–187]. QUR, a flavonoid present in many edible and medicinal plants, is an example of such a compound. QUR has displayed significant potential as both an antioxidant and anti-neuroinflammatory substance, especially when used in treating brain cancer [188]. Research has shown that QUR can effectively block tumor cell growth by inducing necrosis, inhibiting proliferation, promoting apoptosis, and regulating tumor invasion and migration [189–192]. Nevertheless, delivering QUR to the brain requires careful consideration because of its low bioavailability and limited ability to cross the blood-brain barrier. Research has resulted in the creation of a nanocomposite composed of biocompatible polymers, chitosan, and carboxymethyl cellulose. Adding ZnO NPs to this co-biopolymer has greatly improved its mechanical and chemical characteristics, along with its ability to load drugs [193]. Also, the nanocomposite's chemical properties and capacity to cross the blood-brain barrier were enhanced through the addition of GQDs. The nanocomposites of CS/CMC/GQDs/ZnO@QUR exhibit nanoneedle structures of 219.38 ± 5.21 nm average size and a zeta potential of −53 mV. FE-SEM, FTIR, and XRD were employed to analyze the morphology, chemical bonding, and crystallinity of the nanocomposite, correspondingly. Studies on drug release showed that QUR is released gradually over 72 h, indicating a more controlled release compared to other QUR carriers on the market. Moreover, MTT assays performed on U-87 MG and L929 cell lines verified the nanocomposite's powerful anti-cancer effects and reduced toxicity in comparison to free QUR. Table 1 provides an overview of the use of chitosan-enhanced graphene composites in the treatment of cancer.

4.2. Hyaluronic acid

4.2.1. Hyaluronic acid properties

HA is made up of *N*-acetylglucosamine and glucuronic disaccharide units within a linear mucopolysaccharide framework. It is a significant element of the extracellular matrix [218]. A additionally contains hydroxyl and carboxylic groups along with an *N*-acetyl group, allowing for further chemical modifications. Various cell types, including fibroblasts, produce HA [219]. HA is acknowledged for its remarkable ability to attract water, non-toxicity, natural degradability, cell compatibility, and absence of immune reaction, providing it an edge over many other materials [220]. HA-based nanomaterials intrigue researchers for biomedical applications like drug delivery and imaging, particularly in targeting cancer cells with high HA-binding receptors [221]. Following uptake by cancer cells via CD44 receptor-mediated endocytosis, hyaluronidase enzymes break down HA into smaller fragments [222]. The CD44 glycoprotein, present throughout the body, demonstrates significant promise for targeted cancer therapy. Elevated amounts of the CD44 receptor have been found in various cancer types, including colon, ovarian, breast, and squamous cell carcinoma [223]. A significant amount of HA has similarly been utilized as a targeting ligand in the development of tailored drug delivery systems [224–227]. HA-based nanodelivery systems have been modified to boost their capacity to traverse biological membranes, enhance targeting precision, and elevate drug accumulation at specific sites [225–227]. Recent studies show HA may improve targeted anticancer drug delivery, enhance treatment effectiveness, and hinder tumor growth [228]. Conjugating nanocarriers with HA facilitates targeted delivery of anticancer drugs to various cancers, effectively administering medications, inhibiting cell division, inducing apoptosis, and preventing metastasis [228].

Table 1
A summary of the chitosan-modified graphene composites in cancer therapy.

Vehicle/material	The main outcomes of study	Refs.
Graphene composite/chitosan hybrids	A smart drug delivery system using GON with chitosan-modified coatings facilitates pH-sensitive release of doxorubicin at targeted locations, enhancing absorption and efficacy in cancer treatment.	[194]
Ternary graphene oxide/ chitosan/silver nanocomposites	A new and resilient nanocomposite composed of silver nanoparticles created through eco-friendly methods, graphene oxide, and chitosan exhibited significant toxicity towards various cancer cell types.	[195]
Graphene oxide composite modified with EDTA or chitosan	A nanocomposite consisting of graphene oxide blended with chitosan or EDTA exhibited significant anti-cancer properties against MCF-7 breast cancer cells, primarily by inducing apoptosis and stopping the cell cycle in the G0/G1 phase.	[75]
Chitosan hydrogels containing graphene oxide	This study developed a flexible drug/ gene delivery mechanism using a thermosensitive hydrogel to concurrently carry irinotecan and SLP2 shRNA for targeted, ongoing treatment of glioblastoma multiforme, showcasing successful cell delivery, gene inhibition, and therapeutic efficacy across multiple experimental scenarios.	[196]
Chitosan/graphene-modified patterned ITO electrode	An ITO electrode modified with chitosan-graphene was utilized to develop a label-free disposable electrochemical immunosensor for the detection of PSA featuring high sensitivity and selectivity. The sensor exhibited outstanding performance, identifying PSA in human serum samples with a detection threshold of 0.8 pg/mL.	[197]
Chitosan-S-doped graphene-based needle stochastic sensors	Needle stochastic sensors were developed utilizing sulfur-doped graphene and chitosan for precise identification of CA 19-9 and CEA in various biological samples, showing effective validation in gastric cancer patient samples with great accuracy.	[198]
Chitosan-functionalized graphene oxide composites	A targeted cancer therapy drug delivery system incorporating graphene oxide altered with carboxymethyl chitosan, fluorescein isothiocyanate, and lactobionic acid exhibited pH-sensitive doxorubicin release, leading to the death of liver cancer cells while protecting healthy cells, indicating promise for focused cancer treatment.	[199]
Chitosan hydrogels containing graphene nanosystems	A novel injectable hydrogel, formed by merging Pluronic F127 with chitosan and infused with dopamine-reduced graphene oxide (DOPA-rGO), demonstrated effective breast cancer photothermal treatment and antibacterial properties.	[200]
Chitosan nanoparticle loading in graphene oxide structures	A novel approach to drug delivery utilizes chitosan nanoparticles encapsulated in graphene oxide with caffeic acid, demonstrating controlled drug release that is responsive to pH levels. This may be beneficial for focused cancer therapy with ongoing administration for a week.	[201]
Chitosan/poly(lactic acid)/ graphene oxide/TiO2 composite nanofibrous scaffolds	Chitosan/PLA nanofibrous scaffolds infused with graphene oxide/TiO2/ doxorubicin exhibited pH-sensitive drug release and effectively inhibited lung cancer cell proliferation, especially in the presence of a magnetic field.	[202]
Graphene oxide-chitosan composite	Biogenic copper nanoparticles embedded in graphene oxide-chitosan nanocomposites displayed enhanced antibacterial activity against *Escherichia coli* and significant anti-cancer effects on MCF7 breast cancer cells.	[203]
Reduced graphene oxide-chitosan-gold nanoparticle composite	A graphene-based aptasensor incorporating reduced graphene oxide, chitosan, and gold nanoparticles successfully detected breast cancer cells (MCF-7) with high sensitivity and precision, achieving a low detection limit of 4 cells/mL and an extensive linear range.	[204]
Chitosan magnetic-graphene nanostructures	A platform named CMG that combines chitosan and magnetic graphene nanoparticles was developed to concurrently deliver genes/drugs and SPIO, leading to efficient tumor targeting, enhanced MR imaging, pH-responsive doxorubicin release, and potent anticancer effects.	[205]
Chitosan-grafted-poly (methacrylic acid)/graphene oxide nanocomposite	A novel drug delivery system was developed using chitosan-*graft*-poly (methacrylic acid) and graphene oxide, showcasing remarkable biocompatibility, effective doxorubicin encapsulation, and pH-sensitive drug release.	[206]
Magnetic graphene oxide	Magnetic iron oxide nanoparticle-containing graphene oxide nanosheets, altered with chitosan and sodium alginate, demonstrated effective pH-responsive release of doxorubicin, targeted cellular uptake via magnetism, and enhanced photothermal properties.	[207]
Vesicle-chitosan-PEGylated graphene oxide conjugates	Herbal extracellular vesicles, when combined with chitosan and PEGylated graphene oxide, effectively delivered siRNA targeting the estrogen receptor α to breast cancer cells, while neem-derived EVs showed the highest efficacy by specifically targeting the CD44 receptor.	[208]
Green magnetic/graphene oxide/ chitosan/*allium sativum*/ quercus nanocomposite	This study developed a nanocomposite made up of green magnetic graphene oxide, chitosan, *allium sativum*, and quercus to transport doxorubicin to designated targets. The research demonstrated enhanced drug encapsulation, controlled release based on pH levels, and significant anticancer effects in experimental trials.	[209]
Chitosan/graphene oxide-Ag bio-nanocomposite hydrogel beads	The research developed pH-sensitive chitosan/GO-Ag nanocomposite hydrogel beads for the controlled release of doxorubicin. These beads displayed effective drug loading, antibacterial properties, and a gradual release pattern that enhanced with increased GO-Ag nanohybrid content.	[210]
Injectable hydrogel	This study developed a self-healing hydrogel composed of polyaldehyde	[211]

(*continued on next page*)

Table 1 (*continued*)

Vehicle/material	The main outcomes of study	Refs.
	gum Arabic, carboxymethyl chitosan, and graphene oxide loaded with doxorubicin, demonstrating pH-responsive drug release, excellent biocompatibility, and targeted toxicity towards breast cancer cells.	
Reduced graphene oxide	This study developed a hydrogel that reacts to stimuli by integrating chitosan methacrylate, small intestine submucosa methacrylate, and doxorubicin-functionalized reduced graphene oxide for melanoma treatment. It employs NIR light for photothermal therapy and warmth to release doxorubicin, with modeling and assessment conducted in silico and in vitro.	[212]
Chitosan-modified graphene oxide	This study developed ChrGO nanosheets through microwave-assisted reduction for targeted intracellular drug delivery, demonstrating enhanced therapeutic efficacy and combined antitumor effects in HER2-overexpressing breast cancer cells when administered with trastuzumab, leading to significant apoptosis and cell death.	[213]
Chitosan-reduced graphene oxide	This study developed a chit-rGO nanoplatform that is loaded with IR820 dye and doxorubicin, merging chemotherapy with near-infrared light-activated photothermal and photodynamic therapy to demonstrate significant anticancer effects on mouse colon cancer cells.	[214]
Chitosan oligosaccharide-grafted nGO	This study developed a flexible nanoplatform (nGO-COS-CD47/DTIC) for targeted chemo-photothermal therapy of melanoma, exhibiting excellent biocompatibility, efficacy in photothermal treatment, accurate drug delivery, and heightened cancer cell mortality under near-infrared light exposure.	[215]
Chitosan overlaid Fe_3O_4/rGO nanocomposite	This study developed a chitosan-coated nanocomposite of reduced graphene oxide-Fe3O4 for targeted fluorescence imaging and drug delivery in cancer. It demonstrated effective loading of doxorubicin, pH level-based controlled release, enhanced cellular uptake, and improved antibiofilm and antioxidant properties. It may be applied in targeted chemotherapy and various fields.	[216]
Folic acid-conjugated chitosan-functionalized graphene oxide	This study developed a multifunctional FA-CS-GO nanomaterial for imaging-guided photothermal therapy, achieving effective tumor targeting, strong photothermal effects, and complete tumor elimination in vivo, thus preventing relapse.	[217]

4.2.2. Hyaluronic acid-functionalized graphene composites in cancer therapy

Numerous novel drug delivery systems have been created in biomedicine to address issues related to the administration of anticancer medications during chemotherapy [229–232]. Even though modified carriers offer numerous benefits, like solubilizing drugs and extending blood circulation [233–235], their efficacy is often limited due to their inability to target drug distribution [236–238] 36–238] and control the release of the medication [239,240]. Additionally, if there is inadequate cell absorption, the effectiveness of the therapy is significantly diminished [241]. The accumulation of unidentified materials in healthy tissues may lead to serious adverse effects, limiting their use in healthcare settings [242,243]. Following the modification of GO with CMC, the subsequent step entailed blending HA and FI [244]. The GO-CMC-FI-HA complex effectively encapsulated the anticancer drug DOX, achieving a loading capacity of 95 %. It released the drug significantly faster in acidic tumor conditions (pH 5.8) compared to physiological pH 7.4. The complex selectively targeted cancer cells with high CD44 receptors, inhibiting their growth, by utilizing a dual-receptor targeting system with hyaluronic acid and Arg-Gly-Asp peptide for improved drug delivery [245]. The GO-HA-RGD conjugate was characterized, achieving a DOX loading efficiency of 72.9 % (GO, *w*/w = 1:1). It exhibited pH-sensitive and prolonged drug release. Cell toxicity studies indicated that GO-HA-RGD was well-tolerated by SKOV-3 and HOSEpiC cells. The combination of GO-HA-RGD/Dox showed significantly enhanced cytotoxicity in SKOV-3 cells compared to GO-HA/Dox and GO/Dox, with effective uptake via CD44-HA and integrin-RGD endocytosis.

Lung cancer ranks as one of the most fatal cancers globally, owing to its cells' resistance to therapy and their ability to metastasize. Consequently, discovering novel DDS that can surpass MDR or tumor metastasis would result in improved efficacy in cancer therapy [246–248]. To achieve the targeted removal of drug-resistant lung cancer cells, scientists created a Q-Graphene nanoplatform that is modified with HA. This nanoplatform likewise provided an effective method to oversee and follow the delivery of the medication. A- Graphene materials have embraced their latest addition, Graphene. Q-Graphene, a three-dimensional sphere with substantial volume, is closely related to fullerenes because of its average particle size of roughly 80 nm. It possesses an extensive surface area of 55 square meters per gram, in addition to excellent electrical conductivity and remarkable thermal and chemical stability. Prior to 2012, limited research studies focused on the biomedical applications of Q-Graphene. Banks and his team were pioneers in using Q-Graphene modified electrodes for the detection of small compounds [249]. The Q-Graphene drug delivery system successfully accomplished two functions at once, fluorescence imaging and targeted drug delivery, due to the presence of hyaluronic acid and RBITC [250]. Moreover, DOX was incorporated onto the surface of Q-Graphene through π-π stacking technology, serving as a model drug. The fluorescence of DOX was suppressed by Q-Graphene because of its high electron-accepting capacity, which is remarkable. Furthermore, a notable rise in fluorescence was noted following the release of DOX from Q-Graphene. Thanks to the RBITC tagging and the fluorescence quenching and recovery properties of Q-Graphene, it is possible to observe the absorption of nanoparticles and the release of DOX inside cells. Eco-friendly rGO was modified with a novel amphiphilic polymer sourced from HA for precision cancer PTT applications [251]. Initially, the environmentally friendly reduction of GO with L-ascorbic acid was adjusted by taking into account both the near-infrared absorption and the nanomaterials' size distribution. In the subsequent phase, the HA-based amphiphile was utilized to alter rGO. This nanoformulation's capability to target specific cells is demonstrated by the functionalization of rGO, which enhanced its stability, cytocompatibility, and cellular uptake in cells expressing high levels of CD44. Additionally, the HA-functionalized rGO enabled on-demand PTT, resulting in the destruction of cancer cells, thereby highlighting its potential for targeted cancer therapy (Fig. 2).

In the same way as PEG, HA forms a protective layer on nanosheets when combined with NGO [252]. The shell can inhibit medication release from the nanocarrier, decreasing nanosheets' therapeutic effectiveness. Utilizing a redox-responsive system is vital for overcoming the HA barrier and enhancing drug release. A critical parameter indicates the redox state in cancer cells, affecting responses to chemotherapy and radiation, influenced by GSH and other compounds in tissues [252–255]. GSH consists of glutamic acid, cysteine, and glycine

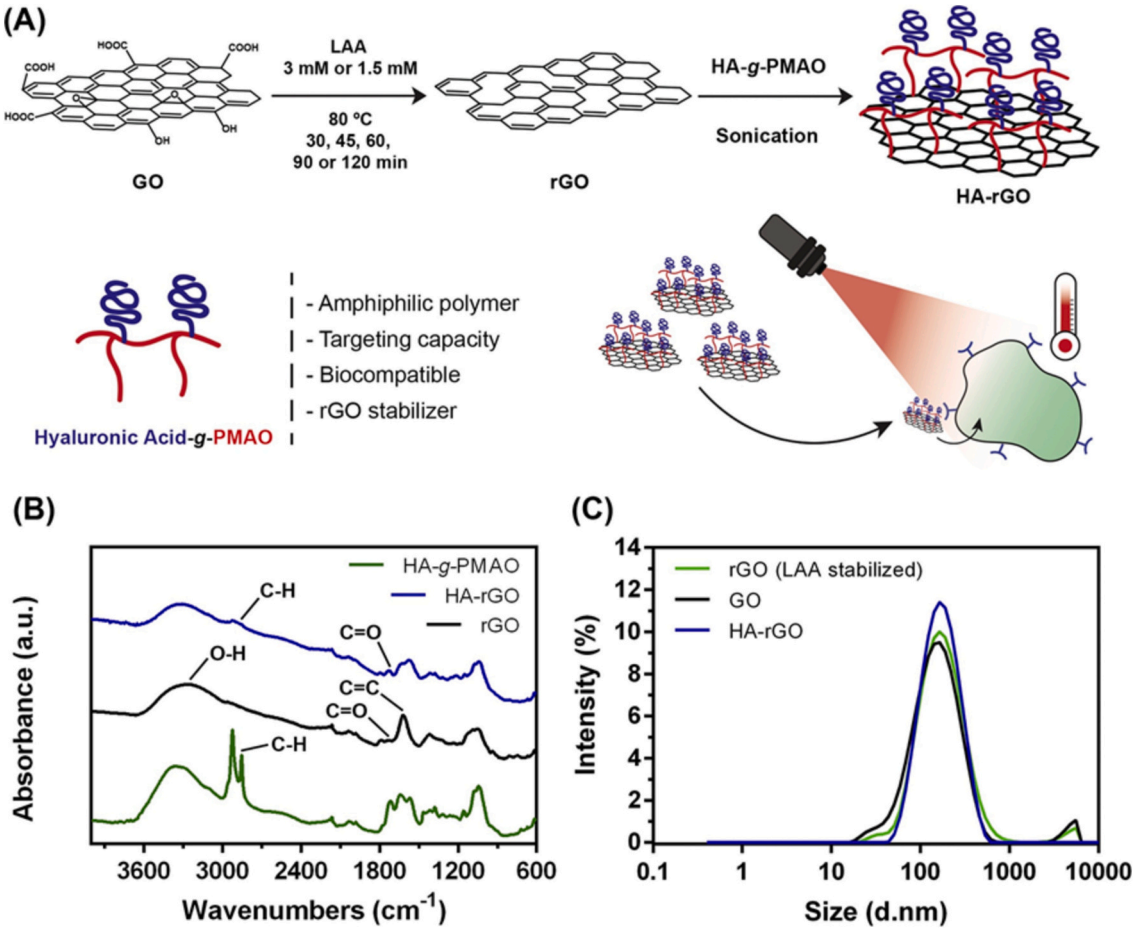

Fig. 2. As well as the preparation and characterization of HA-rGO. This is a schematic illustration of the reduction and functionalization of rGO with HA-g-PMAO, as well as its use in cancer photothermal treatment (A). FTIR spectra of rGO, HA-g-PMAO, and HA-rGO (B) are shown here. The size distribution of GO, rGO treated with LAA stabilization, and HA-rGO (C) using DLS.
Reprinted with permission from Elsevier [251].

structured as a tripeptide. GSH is present in almost all cells throughout the body, and the concentration of GSH within cells is significantly higher than that found outside of them [256,257]. Gefitinib might be delivered to tumors using HA-grafted GO nanosheets, showing excellent physiological stability, significant biocompatibility, and no noticeable adverse effects in mice [258]. Additionally, these nanosheets may serve as a nanocarrier delivery mechanism. Experiments demonstrated that A549 cells absorbed NGO-SS-HA more rapidly via CD44 receptor-mediated endocytosis and released the contents inside the cell. In addition, the release of the drug from NGO-SS-HA was greater when GSH was present than when it was not. The ability of Gefitinib-loaded GO nanosheets to promote cell death, regulate cell proliferation, and impede tumor development in mice with lung cancer was significantly improved. The attachment of NGO-SS-HA to cancer cells facilitated the effective transport of cargo when subjected to redox reactions. CuS and GO were integrated into a complex nanostructure for trio-responsive chemo-phototherapy. DOX was used as the chemotherapy drug while HA served as the targeting agent [259]. In the presentation, the nano-system CuS(DOX)-GO-HA demonstrated its capability to release drugs in response and improve its photothermal activity. The existence of dual photosensitizers resulted in the observation of both hyperthermia and the photodynamic effect, along with effective generation of ROS. The in vivo biodistribution and photothermal profile analysis revealed a significant accumulation and retention of the nanoconstruct within the tumor. Examining tumor size and changes in apoptosis, cell growth, and angiogenesis markers is essential for evaluating the effectiveness of nanoconstructs in stopping tumor development (Fig. 3). Table 2 illustrates the widespread application of HA-modified graphene composites in cancer treatment.

4.3. Alginate

4.3.1. Alginate properties

Sodium alginate, obtained from the ocean, is a biopolymer [274]. It ranks among the most frequently utilized natural substances in different pharmaceutical applications, like intelligent delivery systems and sensors [275,276]. Alginate's molecular structure confirms its classification as a hydrogel, rendered insoluble in water. Sodium alginate appears as a white or yellowish powder, odorless and tasteless [277]. Alginate shows promise as an absorbent, hemostatic wound dressing and is applicable in dentistry, tissue engineering, and cosmetics as an emulsifier [278]. Additionally, alginate possesses anti-inflammatory effects in the stomach and promotes the healing of gastric mucosa. Considering this, it may possess the capacity to protect the stomach and alleviate discomfort. Gastric dressing is formed in the stomach when hydrochloric acid is mixed with sodium alginate. Additionally, alginate may contribute to weight loss, thereby helping to avert obesity [279]. Because of these properties, sodium alginate is an essential component for various applications in diagnosis and sensing fields. As a result, many researchers are engaged in developing nanoparticles using alginate. The quick development of a gel is among the most attractive features of alginate when combined with divalent cations, particularly Ca2+ [280]. Alginate can form stable hydrogels using millimolar quantities of calcium or other divalent cations such as barium or strontium. These positively

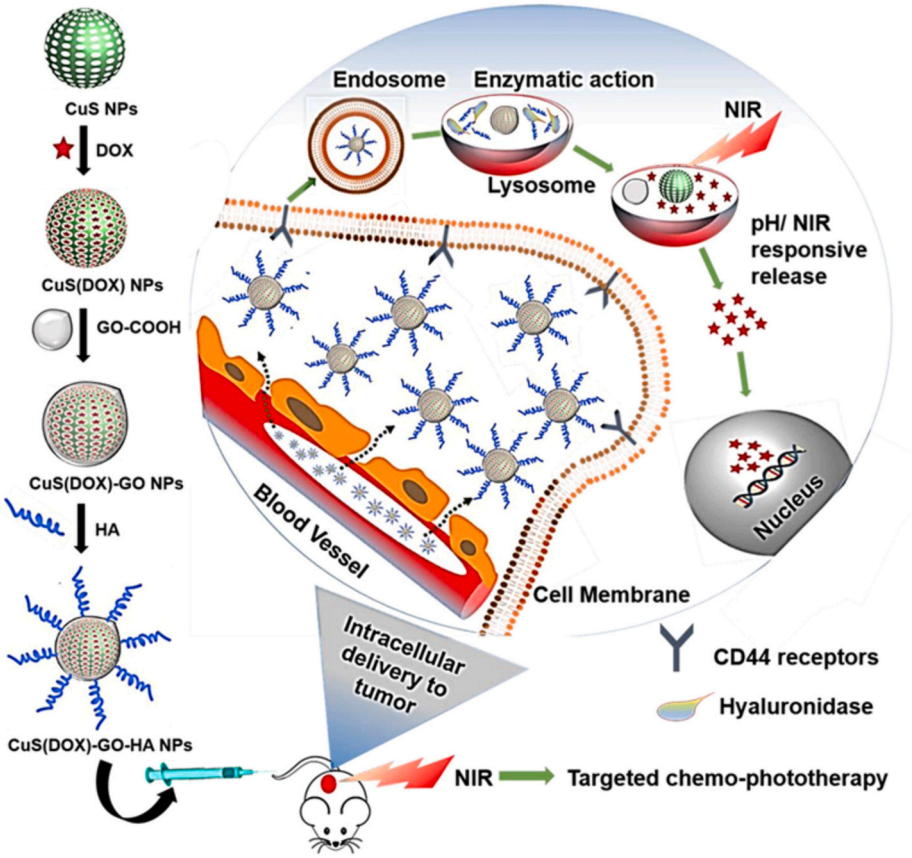

Fig. 3. This is a schematic representation of the method that is used to create guided tri-agent integrated nanoparticles (CuS(DOX)-GO-HA NPs) that are preferentially taken up by the CD44 receptors. Cancer cells undergo apoptosis as a result of targeted chemo-phototherapeutic action, which is caused by a combination of enzymatic activity carried out within cancer cells and NIR-responsive behavior.
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charged ions function to form connections among G units [281]. This gelation characteristic enables cells to be confined in a physiological setting, guaranteeing uniform distribution throughout the matrix [282,283]. The mechanical properties of the alginate beads can be affected by the composition and concentration of the polymer. Ouwerx et al. [284], demonstrated that the elasticity of the bead is constrained by the alginate concentration in the eq. $E = KC^2$, where E denotes Young's modulus and K is the specific constant for alginate. This was demonstrated when the Young's modulus of alginate beads created with 0.1 M calcium rose in proportion to the square of the alginate concentration. Moreover, a rheological analysis demonstrated a positive relationship between the concentration of guluronic acid and the elasticity of alginate hydrogels [285]. Furthermore, it was shown that the kind and level of the gelling cation [284] also influence the alginate matrix.

4.3.2. *Alginate-modified graphene composites in cancer therapy*

The research focuses on explaining a novel framework composed of graphene oxide nanosheets, calix [4] arene supramolecules, silk fibroin proteins, cobalt ferrite nanoparticles, and alginate hydrogel (GO-CX [4]/SF/CoFe2O4/Alg) [286]. The scaffold demonstrated effective performance with Hu02 cells, showing cell viability rates of 85.23 %, 82.78 %, and 80.18 % after 24, 48, and 72 h, respectively. Conversely, BT549 cancer cells displayed anti-cancer characteristics, demonstrating viability rates of 65.79 %, 60.45 %, and 58.16 % during the specified periods. The combination also inhibited the growth of *E. coli* and *S. aureus*, showcasing its potential as an antibacterial agent. It exhibited a minimal hemolytic impact and reduced the development of *P. aeruginosa* biofilm. The technique of three-dimensional cell culture can mimic tumor pathophysiology, influencing gene expression, cell functions, and internal signaling. By promoting cell interactions and aiding in attachment and growth, it enhances the development of efficient drug screening models. Graphene, cellulose acetate, and sodium alginate are mixed at low temperatures to create a porous scaffold structure intended for the formation of ovarian cancer spheroids, with graphene nanosheets enhancing cell growth and spheroid formation [287]. The accumulation of the tumor mass enhances ROS generation, whereas a lack of oxygen and nutrients raises the production of HIF-1α and VEGF. Metastasis of liver cancer is an important concern associated with colon cancer. After the removal of colorectal cancer, it is crucial to deliver targeted medication to the colon. Conventional approaches face issues such as controlling the release rate and achieving targeting accuracy. This research introduces a colon-specific drug delivery system utilizing sodium ALG and GO, which includes the anticancer medication 5-FU [288]. The results show that the current drug delivery method exhibits lower toxicity levels and enhanced controlled-release properties, leading to improved accuracy in targeting the colon. GO-ALG/5-FU notably inhibited tumor growth and liver metastases, leading to an increased survival rate in the treated mice (Fig. 4).

4.4. *Cellulose*

4.4.1. *Cellulose properties*

Cellulose is a naturally occurring polymer prevalent in the cell walls of plants, algae, fungi, and bacteria [289–291]. Both BC and PC are composed of unbranched, parallel-stacked glucose units linked by β(1–4) chains. Generated by aerobic bacteria, BC is famous for its remarkable purity, compatibility with biological systems, high crystallinity (60–80 %), and its extremely fine nanofibrous architecture

Table 2
Versatile function of HA-modified graphene composites in cancer therapy.

Material	The main outcome of study	Refs.
HA-conjugated nitrogen-doped graphene quantum dots	Blue fluorescent nitrogen-doped graphene quantum dots (N-GQDs) were fabricated through a simple hydrothermal technique utilizing citric acid and diethylamine, effectively marking and targeting human breast cancer cells by binding with hyaluronic acid.	[260]
HA-functionalized reduced graphene oxide	rGO integrated with IR780 and enveloped in hyaluronic acid forms a pH-sensitive drug delivery system that transports doxorubicin, enhancing targeted photothermal, photodynamic, and chemotherapy approaches on U87 glioblastoma cells with high efficacy and low toxicity.	[261]
HA-graphene quantum dot	GQD covered with hyaluronic acid serve as biocompatible carriers for drugs and imaging agents targeting cancer cells, effectively focusing on HeLa cells with proficient drug loading and specialized imaging capabilities.	[262]
Magnetic graphene oxide	The CDHA-MGO nanocomposite combines β-cyclodextrin-hyaluronic acid polymers with Fe_3O_4-graphene oxide, creating an adaptable drug delivery platform with effective doxorubicin encapsulation, exceptional NIR photothermal responsiveness, and targeted chemo-photothermal treatment for hepatoma cells.	[263]
N-doped graphene quantum dot and mesoporous silica nanostructures	The study introduces dual-function MSNPs coated with blue fluorescent N-graphene quantum dots and hyaluronic acid, designed for targeted delivery of DOX to cancer cells and concurrent imaging within HeLa cells.	[264]
HA-functionalized GO	The development of a multifunctional GO nanoparticle system, integrated with HA, DOX, and Ptx, alongside modified iron oxide nanoparticles, facilitates targeted cancer therapy and magnetic hyperthermia, demonstrating improved efficacy in specifically lowering tumor cell viability in CD44-expressing breast cancer cells.	[265]
Fe_3O_4-graphene oxide nanostructures	The study introduces a hybrid nanomaterial (MGO@CD-CA-HA) that integrates chemotherapy and photothermal therapy through a coating of β-cyclodextrin-cholic acid-hyaluronic acid polymer over Fe3O4-graphene oxide. This nanocarrier effectively transports drugs to liver cancer cells through multiple pathways, possesses a significant ability to load camptothecin, and successfully inhibits tumors in both laboratory environments and living organisms, demonstrating potential for treating hepatocellular carcinoma.	[266]
HA-functionalized graphene oxide materials	Dimensions smaller than 100 nm Transport of Ce6 as a photosensitizer Initiation of photodynamic treatment Attaching to HA receptors located on the exterior of cancer cells	[267]
HA-modified graphene oxide materials	The creation of a probe utilizing HA-GO nanostructures and infused with Cy3-tagged antisense miR-21 PNA probes in breast cancer. Decrease in the development and spread of cancer cells Induction of apoptosis	[268]
HA-modified graphene hybrid materials	HA-GO nanohybrids incorporating HA molecules were developed for the pH-responsive delivery of DOX, demonstrating enhanced loading efficiency, selective toxicity towards HepG2 cancer cells, and superior tumor suppression in vivo.	[269]
HA-modified and metformin-loaded graphene oxide nanostructures	Focused administration of metformin and binding to CD44 receptors on cancer cell surfaces to inhibit tumor cell progression. Inhibition of EMT Increased expression of E-cadherin Decrease in stemness	[270]
HA nanogel	The study introduces a blend of graphene-doxorubicin conjugate and hyaluronic acid nanogel to facilitate controlled drug release through the incorporation of light-responsive and pH-sensitive elements. This method provides thermo-chemotherapeutic benefits, real-time visualization, and enhanced treatment results for lung cancer cells while reducing damage to healthy cells.	[271]
HA-glutathione-stabilized gold nanostructures/graphene oxide	The theranostic system HG-GNCs/GO-5FU, resembling a book, includes hyaluronic acid-glutathione conjugate stabilized gold nanoclusters combined with graphene oxide and 5-fluorouracil, providing diverse functions like targeted cancer treatment, controlled drug delivery, and a range of chemotherapy, photothermal, and photodynamic therapies. This system features enzyme and light activation for imaging and therapy, enhancing tumor targeting and minimizing damage to healthy cells.	[272]
HA-modified GO	The MIT/HA-GO/Pluronic nanosheets possess targeted chemo-photothermal characteristics and effectively transport MIT to address MDR in cancer cells. These nanosheets utilize pH and NIR laser-triggered release mechanisms to ensure stability in blood and targeted drug delivery to tumor cells, showing increased cytotoxicity, better drug retention, and enhanced tumor suppression in vivo, particularly focusing on drug-resistant MCF-7/ADR cells.	[273]

[292,293]. PC, originating from multiple plants, provides financial advantages and sustainability, featuring unique attributes such as robust mechanical properties and biocompatibility, which render it ideal for tissue engineering and drug delivery applications [294]. Resources obtained from forests are likewise considered renewable [295]. Cellulose pulp is economically significant and is essential in multiple sectors, including cotton textiles, paper, and pulp, while also being utilized in emerging biomedical applications. Global production of cellulose pulp is approximately 180 million tons annually, with expected growth in the future [296,297]. The difficulty in distributing cellulose in water stems from its extensive hydrogen-bonding network, which results in strong packing among the chains [298]. Multiple techniques have been developed to convert untreated cellulose into readily soluble varieties to address this problem [299,300]. Transforming cellulose into nanocellulose enhances material characteristics. This renewable bio-nano particle boasts various applications, demonstrating strong affinity, stability, mechanical strength, and a large surface area—all advantageous both economically and environmentally [301,302]. The nanocellulose category comprises CNCs, CNFs, and BC, with each type possessing

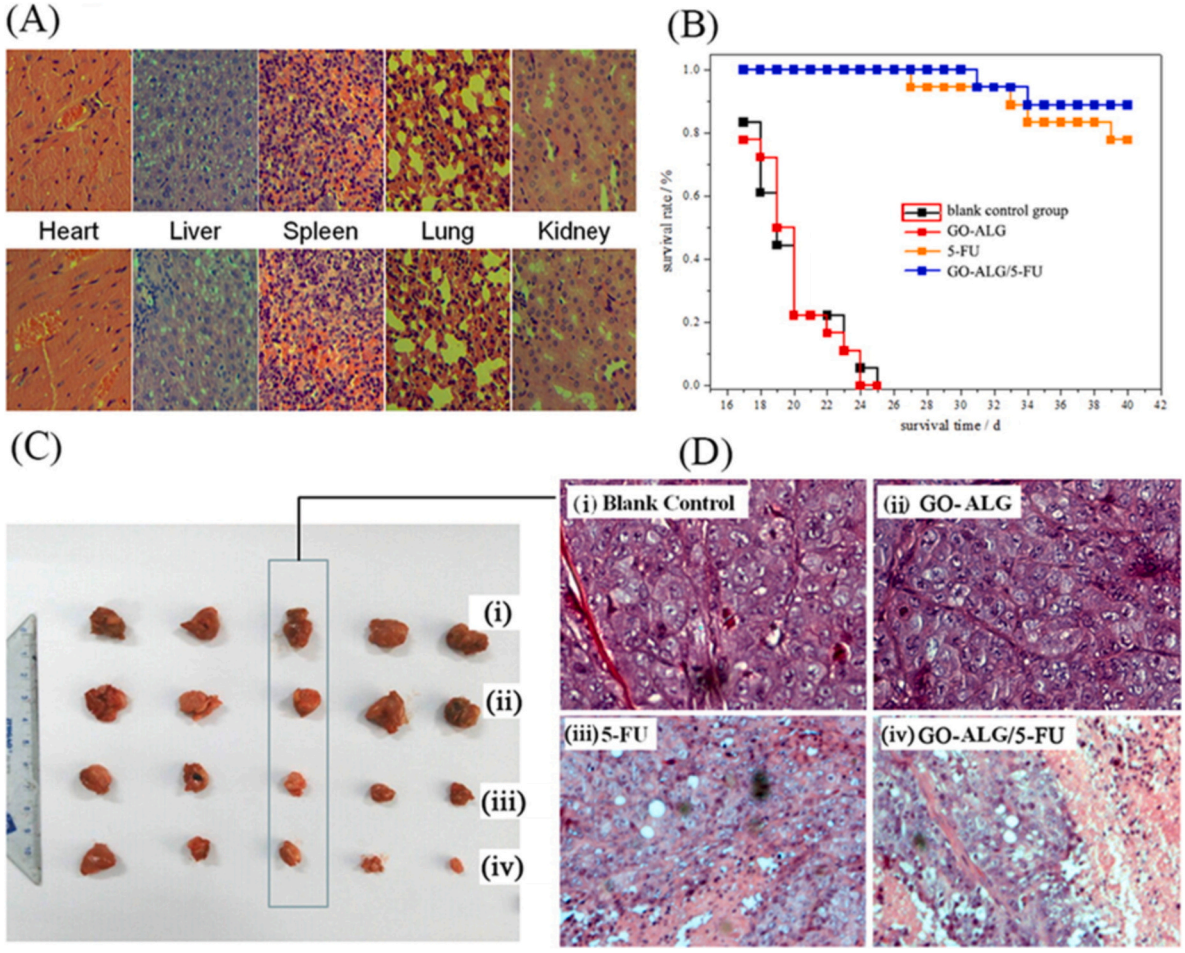

Fig. 4. (a) Representative organ histology from mice, with the control group shown in the top row and the GO-ALG/5-FU-injected group in the bottom row. (b) Kaplan-Meier analysis is used to compare the survival curves between the different groups. Images (c) and (d) display H&E staining of the treated tumors, along with representative photographs of the tumors.
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distinct properties [303]. The literature thoroughly discusses both conventional and environmentally-friendly techniques for generating nanocellulose from lignocellulosic biomass [304].

4.4.2. *Cellulose-modified graphene composites in cancer therapy*

Cellulose derivatives such as sodium carboxymethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose are widely studied for their efficacy in drug delivery [305–307]. CMC is acknowledged for its suitability with living beings, capacity for natural degradation, non-harmful effects on health, and remarkable film-forming properties. It also has a strong ability to encapsulate insoluble and active compounds, rendering it a reliable delivery system for anticancer drugs [308–310]. Moreover, CMC can regulate drug distribution, extend engagement with cancer cells, minimize side effects, enhance cancer treatment effectiveness, and boost medication uptake [311,312]. Amino groups are incorporated into GO, forming GO-ADH, which combines with CMC to create the GO-CMC complex, used as a drug delivery system linked with DOX [313]. A successful GO-CMC complex was confirmed via TEM, FT-IR, and zeta potential assessments. The drug released at 65.2 % in pH 5.0, demonstrating pH responsiveness. The MTT assay evaluated effects on Hela and NIH-3 T3 cells. Nanocomposite hydrogels were produced using green chemistry [314]. The hydrogels were encapsulated within dual nanoemulsions to act as carriers that react to pH alterations for curcumin, a possible anticancer medication. The nanoemulsion comprising layers of water, oil, and bitter almond oil functioned as a protective barrier to control the drug's release. Zeta potential assessments and differential light scattering techniques were employed to assess the size and stability of the curcumin-loaded nanocarriers. FTIR spectroscopy, XRD, and FESEM techniques were used to examine the intermolecular interactions, crystalline structure, and morphology of the nanocarriers. These hydrogels showed significant improvements in drug loading and entrapment efficiencies compared to previous curcumin delivery systems. The nanocarriers demonstrated pH-sensitive release in in vitro experiments, with curcumin being released more rapidly at lower pH values. MTT assays indicated that the nanocomposites demonstrated higher toxicity to MCF-7 cancer cells than CMC, CMC/RGO, or free curcumin. Flow cytometry confirmed apoptosis in MCF-7 cells treated with these nanocarriers (Fig. 5).

4.5. *Starch*

4.5.1. *Starch properties*

Starch serves as the primary energy source for the body's functions. Certain starches were previously believed to be processed by the digestive system [315], but recent studies have shown a type that cannot be deconstructed in the small intestine [316,317]. This starch was first named RS by Englyst et al. [316] in 1982. In 1991, the European Concerted Action verified that the small intestine is not involved in the digestion and absorption of RS. Instead, it reaches the colon and is fermented by gut bacteria to varying degrees [318]. In 1992, the Food and Agriculture Organization of the United Nations established the term RS as an abbreviation for starches and their degradation products that are

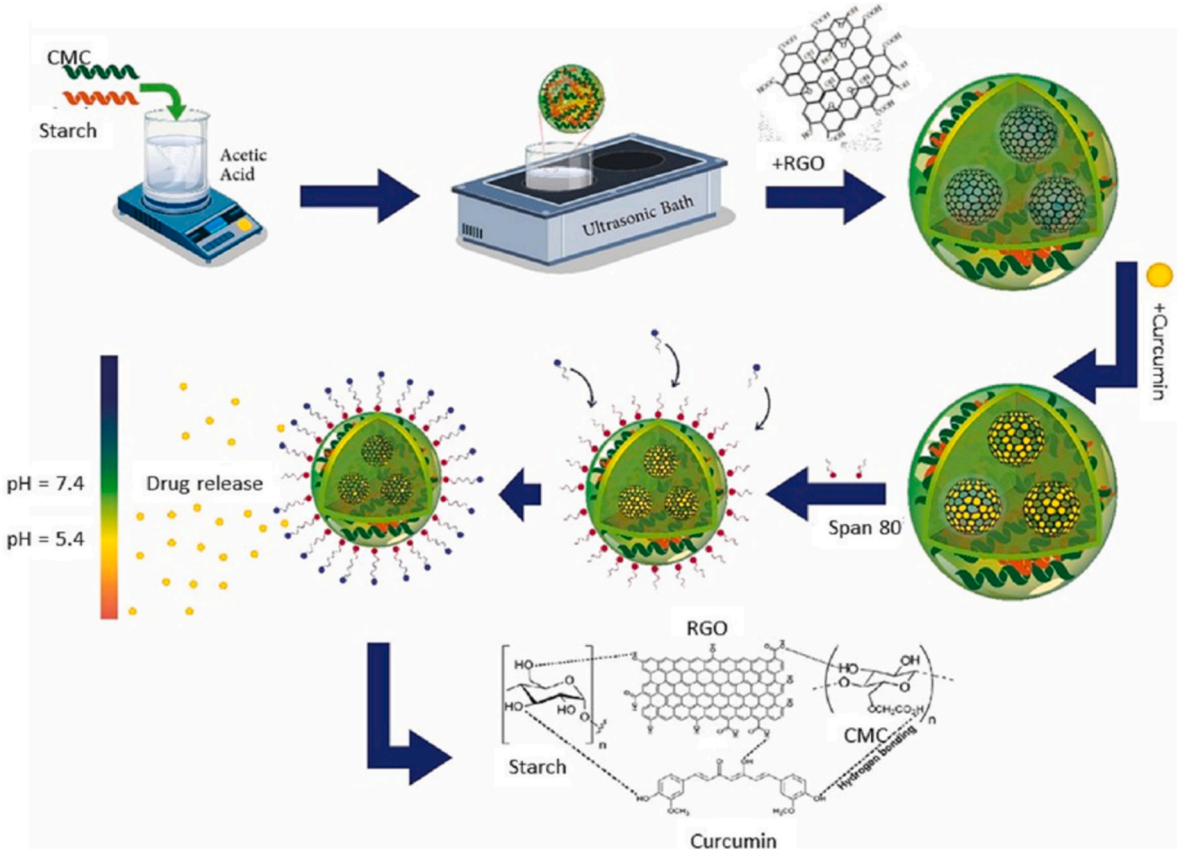

Fig. 5. This diagram illustrates the several phases that are involved in the creation of CMC/starch/RGO/Cur nanocarrier. Reprinted with permission from Elsevier [314].

not digestible in the small intestine of healthy people [319].

4.5.2. *Starch-modified graphene composites in cancer therapy*

Nanomaterials for drug delivery are becoming increasingly favored due to their targeted delivery, high effectiveness, and regulated release, proving to be effective in treating diseases [320,321]. Enhancing drug effectiveness relies on increasing nano-carrier adsorption strength. Graphene's flat structure and delocalized electrons offer a larger surface area, promoting stronger interactions and superior drug encapsulation compared to traditional materials [322]. Previous research has explored the use of EGO as nanoscale carriers for drug delivery in biological systems [323,324]. However, the instability of EGO in physiological conditions has limited its broader application in the field. This emphasizes the ongoing need to develop graphene nano-carriers with targeted functions to enhance drug delivery. A simple, eco-friendly method has been developed for producing starch-modified graphene nanosheets (starch-GNS). This technique employs soluble starch to reduce exfoliated graphene oxides and serves as a functionalization agent, stopping the aggregation of graphene nanosheets [325]. The generated starch-GNS exhibited remarkable biocompatibility, essential for its application in biomedicine. Cell toxicity assessments showed no adverse effects on SW-620 cells at concentrations as low as 200 μg/mL. HCPT@starch-GNS, a substance infused with HCPT anticancer medication, demonstrated excellent drug-loading abilities. The composite was employed for cell imaging and drug delivery research. SW-620 cells took up the HCPT@starch-GNS composite via endocytosis, exhibiting increased toxicity because of cellular acidity and the presence of diastase. The starch-driven and pH-responsive mechanism for extended release may enhance treatment effectiveness. The effective synthesis was accomplished for the nanohybrid consisting of photoluminescent graphene quantum dots and bio-metal organic framework (GQDs@Bio-MOF). The BET analysis indicated that GQDs@Bio-MOF possesses an average pore size of approximately 11.97 nm, which renders it appropriate for capturing the anticancer medication 5-Fu due to its nano-scale porosity [326]. The encapsulation efficiency of 5-Fu within this configuration was around 42.04 %, showcasing a loading capacity of roughly 4.20 % (5-Fu@GQDs@Bio-MOF). Furthermore, a sample coated with starch biopolymer (St@5-Fu@GQDs@Bio-MOF) showed a pHPZC value of 4.67. SEM analysis showed that the microspheres of St@5-Fu@GQDs@Bio-MOF are round and have an approximate diameter of 2 μm. Laboratory tests for drug release indicated that St@5-Fu@GQDs@Bio-MOF exhibited a superior release profile, with approximately 62.3 % of the encapsulated 5-Fu released within 96 h. The Higuchi model provides the best fit for the release kinetics of 5-Fu, showing an R2 value of 0.9884. The findings from in vitro cytotoxicity experiments indicated that St@GQDs@Bio-MOF may serve as a safe carrier, maintaining cell viability at or above 84 % (Fig. 6).

4.6. *Dextran*

4.6.1. *Dextran properties*

In 1861, Louis Pasteur discovered dextran, derived from bacteria that generate slime [327]. In 1878, Van Tieghem referred to these bacteria as *Leuconostoc mesenteroides* [328]. Gram-positive cocci such as Leuconostoc and Streptococcus are capable of producing dextran through fermentation processes [329]. Dextran is a branching glucan with α-1, 6 glycosidic linkages of glucose [330]. It comprises branches from α-1, 2, α-1, 3, and α-1, 4 linkages, with the bacterial strain influencing the branching degree and their characteristics at positions 2, 3, and 4. Dextran is primarily synthesized outside of cells by specific lactic acid bacteria that utilize the enzyme dextransucrase to transform sucrose. This enzyme facilitates the transfer of D-glucopyranosyl residues

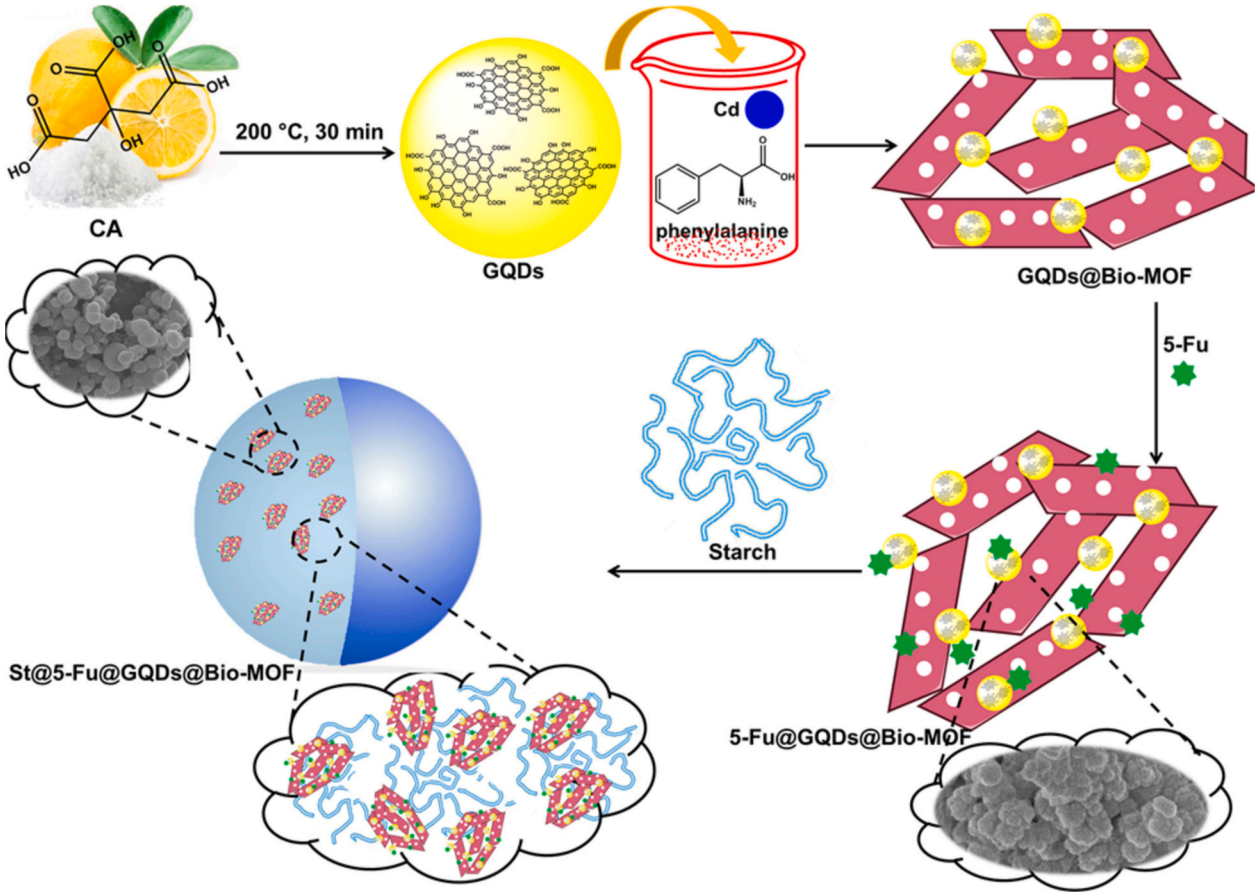

Fig. 6. For the synthesis of the St@5-Fu@GQDs@Bio-MOF microspheres, the following schematic method has been proposed. Reprinted with permission from Elsevier [326].

from sucrose to dextran [330,331]. In recent years, dextran-modified nanoparticles have become widely used in cancer treatment. A nanocarrier composed of dextran and aspirin has been developed for oral application [332–334]. It may reduce inflammation and alter gut microbiota to assist in the treatment of primary colorectal cancer [335]. The polymeric micelles were modified with hyaluronic acid and dextran for the concurrent delivery of doxorubicin and ursolic acid to enhance ROS levels, resulting in mitochondrial impairment and reduced mitochondrial membrane potential in cancer therapy [336]. Iron-crosslinked dextran nanogels have been created for cancer therapy by focusing on tumor-associated macrophages, highlighting their function in reshaping the tumor microenvironment [337]. Moreover, dextran can create complexes with docetaxel for application as an anti-cancer therapy, enabling it to target and suppress the growth of breast cancer at the tumor site [338].

4.6.2. Dextran-modified graphene composites in cancer therapy

Conventional chemotherapy medications have been extensively utilized to provide effective cancer therapy in medical environments. On the other hand, cancer cells can develop drug resistance due to the activation of MDR transporters, which frequently reduces the effectiveness of anticancer therapies [339]. Recent research indicates that nano drug carriers can efficiently transport medications into cells, enhancing the effects of cancer treatments [340]. Nanomicelles and nanoparticles are under investigation for their capability to transport anticancer medications [340,341]. Recently, there has been significant interest in the possible application of GO as an innovative technique for drug delivery [342]. NGOs provide benefits compared to traditional drug delivery systems like nanomicelles, including ease of loading hydrophobic medications and substantial drug carrying capacity. For instance, Chen and his team created a nanohybrid consisting of NGO and DOX, which demonstrated a DOX loading capacity of 2.35 mg/mg of NGO [343]. Additionally, Wu and associates discovered that the DOX-loaded NGO system significantly enhanced the accumulation of DOX in drug-resistant MCF-7/ADR cells [344]. A nanohybrid made of NGO and dextran was developed to aim at drug-resistant MCF-7/ADR cells [345]. The formation of NGO-HDex included the use of HDex and unmodified graphene oxide via π-π interactions to produce a graphene-based nanohybrid. NGO-HDex demonstrated enhanced durability under normal body conditions when compared to its unfunctionalized counterparts. Additionally, NGO-HDex successfully loaded the anticancer drug DOX, achieving a drug loading capacity of 3.4 mg/mg NGO and releasing it with high efficiency in a pH-dependent way. Cell viability tests indicated that NGO-HDex caused less damage to MCF-7/ADR cells than the original NGO. However, DOX-loaded NGO-HDex showed greater effectiveness in eradicating these cells than free DOX, as it facilitated increased DOX accumulation inside the cells. To assemble MGO nanoparticles layer by layer, charged polyelectrolytes are repeatedly deposited on the MGO surface. This technique is known as layer-by-layer assembly. Consequently, this initiative seeks to develop adaptable polyelectrolyte multilayer (PEM) coatings for drug delivery on MGO surfaces. LbL assembly has the capability to attain high drug loading, regulate drug release, and aim at specific locations, all while preserving the nanoscale structure intact [346,347]. Only a few studies focus on LbL assembly and layer thickness for responsive targeted drug release. Polyelectrolytes, characterized by ionizable groups like polyanions and polycations, were initially researched in the 1940s and 1960s, leading to increased interest in various biological applications [348,349]. A novel system was developed using a layer-by-layer (LbL) assembly technique, consisting of AND and CNC stacked on chemically modified MGO [350].

The system entails the engagement of alternating layers of cationic AND and anionic CNC with MGO via electrostatic interaction to produce a nanocomposite known as MGO-AND/CNC. This nanocomposite employs π-π stacking and hydrogen bonding to encapsulate the cancer-treatment medication CUR. After testing various concentrations of MGO and AND/CNC, the optimal hydrodynamic particle size was determined to be 158.0 nm. Zeta potential recorded at −45.9 ± 6.9 mV, with encapsulation efficiency at 86.4 ± 4.7 %. Examined the nanocomposite through techniques such as FTIR, SEM, TEM, AFM, DLS, and zeta potential analysis. Research on drug release indicated that MGO-AND/CNC discharges curcumin more quickly in an acidic environment compared to a neutral gut pH. A drug-impregnated MGO-AND/CNC demonstrated effective induction of HCT116 cell death in a cytotoxicity assay when subjected to NIR laser illumination. To form a dependable and biocompatible layer of dextran on graphene oxide (GO-DEX), DEX was bonded to the nano-GO sheets using covalent connections. The GO-DEX generated showed no adverse effects on the 4T1 mammary cancer cells, even at elevated doses reaching 300 μg/mL. Furthermore, AS1411, an ssDNA aptamer, was attached to the hydroxyl groups of DEX on GO-DEX to form GO-DEX-Apt [351]. This molecule selectively attaches to nucleolin, enhancing the uptake of this compound within cells. Curcumin, a polyphenol obtained from turmeric known for its anti-cancer properties, was incorporated into GO-DEX and GO-DEX-Apt through π-π stacking interactions, achieving a loading capacity of approximately 29 wt%. The mix of GO-DEX-Apt-CUR showed greater cytotoxicity and was efficiently absorbed by 4T1 and MCF-7 cancer cells with increased nucleolin levels. The effectiveness was confirmed through fluorescence microscopy and flow cytometry methods. A new method employs dextran as a reducing agent for the synthesis of reduced graphene oxide nanoparticles [352]. Dex achieves direct attachment to rGO through hydrogen bonds, forming rGO/Dex nanoparticles that exhibit strong biocompatibility and deliver anticancer drugs for photochemotherapy. These nanoparticles encapsulate DOX, creating rGO/DOX/Dex formulations. Furthermore, RGD oligopeptide is included to improve cellular uptake via αvβ3 integrin recognition, enhancing the efficacy of localized chemotherapy combined with NIR photothermal therapy compared to standard chemotherapy.

4.7. Pectin

Earlier research has shown that drug carriers utilizing polymer-functionalized GO significantly enhance the distribution of drugs across the body. Functionalization contributes to improving biocompatibility, drug loading, and release efficiency, resulting in this enhancement [353,354]. It has been found that altering GO with polymers is the most effective approach to minimize aggregation, resulting in enhanced stability and performance [355]. Initially, Liu and associates outlined the method of modifying GO with polymers, successfully modifying GO using PEG to transport SN38 [356]. Subsequently, numerous research studies on this subject have emerged. An example involves the development of a gelatin-conjugated graphene sheet by An and associates designed for the efficient delivery of methotrexate [357]. Mianehrow and associates examined ways to enhance GO stability in saline conditions by utilizing hydroxyethyl cellulose [159]. Furthermore, Lei and colleagues developed GO modified with chitosan and sodium alginate, leading to improved stability, water solubility, and drug loading capacity [354]. A new PEC-conjugated magnetic GO nanocarrier designed for the efficient delivery of paclitaxel has been successfully developed [358]. The nanocarrier showed improved stability and drug loading capacity. The pH-responsive delivery study revealed increased drug release in cancer cell endosomes compared to normal conditions, while cytotoxicity tests confirmed high cell viability and nanohybrid compatibility.

5. Conclusion

The present review demonstrates significant advancements in developing drug carriers for cancer therapy utilizing polymer-functionalized GO. These transporters have shown considerable promise due to their enhanced capability to engage effectively with biological systems, greater capacity for drug retention, and improved effectiveness in drug release, addressing key challenges in conventional chemotherapy like absence of specific targeting and overall toxicity. Nonetheless, the issue remains in making sure that nanomaterials are biocompatible over extended periods and in minimizing their possible toxicity. This highlights the significance of ongoing research regarding the interaction of these nanomaterials with biological systems. Boosting the manufacturing of graphene-based nanocomposites for medical applications is difficult because of technical and regulatory challenges. The regulatory environment for medical products based on nanotechnology is intricate, resulting in postponements in transitioning from lab innovations to market-ready offerings. Additionally, it is crucial to ensure quality while increasing production for extensive clinical application. In the future, employing graphene composites for precise delivery systems could revolutionize cancer therapy by minimizing side effects and enhancing treatment outcomes. Exploring hybrid nanosystems of graphene and biocompatible materials may enhance multifunctional drug delivery. Prioritizing clinical trials is essential to assess safety and efficacy for integration into oncology treatments, improving patient care.

Graphene shows promise in biomedicine, particularly for cancer treatment, due to its surface area and conductivity, but challenges like hydrophobicity and cytotoxicity need to be addressed for biocompatibility. Utilizing carbohydrate polymers such as chitosan and hyaluronic acid offers an effective approach to tackle these issues. This approach improves graphene's dispersal in biological contexts and allows for the creation of advanced drug delivery systems with customized, pH-sensitive release characteristics. Such accuracy is essential for traversing the intricacies of the tumor microenvironment and obtaining targeted therapeutic outcomes while reducing off-target toxicity. Various functionalization methods like covalent conjugation, layer-by-layer assembly, in situ polymerization, and nanoparticle encapsulation create multifunctional composites for diverse applications. The creation of these composites generally includes merging graphene or its derivatives with carbohydrate polymers using either chemical or physical methods. Chemical functionalization utilizes the reactive functional groups on graphene oxide, like carboxyl and hydroxyl groups, to create covalent bonds with chitosan and hyaluronic acid. As an alternative, physical blending guarantees consistent distribution through ultrasonication or mechanical agitation. Layer-by-layer construction produces strong composites through the sequential application of polyelectrolyte layers made of positively charged chitosan and negatively charged graphene oxide. In situ polymerization forms uniform polymer coatings directly on the surface of graphene. Encapsulation methods incorporate drug-encapsulated nanoparticles into a carbohydrate matrix, effectively merging their benefits for regulated drug release. These carefully designed composites provide a multifaceted strategy for cancer therapy, enabling precise drug delivery, pH-responsive release, and improved therapeutic effectiveness. Additional investigation aimed at improving synthesis techniques, increasing production capacity, and performing thorough in vivo studies is necessary to confirm their safety and therapeutic efficacy. Carbohydrate polymer-enhanced graphene composites offer an innovative and interdisciplinary approach to tackle the issues in contemporary oncology, leading to tailored and efficient cancer treatments.

Graphene's exceptional blend of structural, physicochemical, and biological characteristics sets it apart from other carbon-based nanomaterials, positioning it as a prime candidate for cancer treatment. Its flat, two-dimensional form offers a large surface area for effective drug loading, and the incorporation of oxygen-bearing functional groups on graphene oxide allows for easy adaptation with biomolecules,

improving biocompatibility and engagement with biological systems. This straightforward functionalization, along with enhanced aqueous dispersibility relative to carbon nanotubes and other nanoparticles, makes graphene an adaptable platform for biomedical uses. The surface chemistry of graphene enables controlled drug release using π–π stacking and hydrogen bonding for effective targeting of acidic tumor environments. Its intrinsic photothermal characteristics enable combined therapies that trigger apoptosis in cancer cells when exposed to near-infrared light. The optoelectronic properties of graphene enable multifunctional platforms for drug delivery, imaging, and therapeutic observation. Functionalization with carbohydrate polymers such as chitosan enhances dispersibility and cellular absorption via electrostatic interactions, while also promoting targeted release. Hyaluronic acid attachment helps in directing cancer cells that overexpress CD44, enhancing biocompatibility and treatment efficiency. Other polysaccharides like alginate and dextran further enhance stability and circulation of these systems. The combination of graphene and carbohydrate polymers creates advanced therapeutic platforms that tackle the complex issues of cancer therapy. These composites present a hopeful approach for tackling drug resistance, reducing off-target effects, and ultimately enhancing patient outcomes. Moreover, graphene is inflexible, and modifying it with carbohydrate polymers can enhance its ability to be internalized in cancer cells. The graphene composites can be harmful to cancer cells at elevated concentration levels. Hence, this combination has the potential to enhance cancer treatment. Regarding the clinical use of the existing materials, several steps remain to be completed before their implementation in the clinic. Despite the high toxicity of graphene and its derivatives, which makes them unsuitable for clinical use, modifying them with carbohydrate polymers can enhance their biocompatibility. Nevertheless, one of the inquiries concerns the metabolism and their breakdown within the body. Additionally, the way their metabolism takes place in the body and whether there are any negative effects from their degraded substances over the long term. Furthermore, it must be assessed that these frameworks are advantageous for the administration of medications or genes in cancer treatment.

The limited research on agarose-modified graphene for cancer treatment offers an exciting opportunity for novel exploration. Future studies could explore its potential as a drug delivery method by leveraging the biocompatibility and gel-forming properties of agarose alongside graphene's large surface area and drug-loading abilities. Developing pH-sensitive agarose-graphene hydrogels for controlled drug release, especially targeting the acidic tumor microenvironment, or designing systems for the simultaneous administration of hydrophobic and hydrophilic drugs could significantly enhance treatment outcomes. Moreover, the stabilizing attributes of agarose could be utilized to create graphene-based nanomaterials for photothermal treatment, enabling more targeted and safer cancer interventions, while its hydrophilic nature may enhance the generation of reactive oxygen species in photodynamic therapy. The combination of these substances could enable the development of 3D tumor models for drug testing or injectable hydrogels for focused therapy, thereby reducing systemic negative effects. Furthermore, their application in immunotherapy may be investigated, which includes the delivery of immunotherapeutic substances or altering the tumor microenvironment to boost immune cell attraction. Agarose-graphene composites can be used in cancer diagnosis via biosensors, harnessing agarose's capacity to immobilize biomolecules and graphene's exceptional electrical conductivity. Thorough studies on toxicity and biodegradability are crucial for safe use, involving particular modifications to functional groups to improve safety without compromising therapeutic effectiveness. These perspectives suggest that agarose-modified graphene could serve as a flexible platform in cancer treatment, addressing current limitations and enabling innovative therapies.

The chemistry of carbohydrate polymer-altered graphene nanocomposites significantly enhances their application in cancer treatment by optimizing the inherent features of graphene and addressing common challenges in drug delivery, targeting, and biocompatibility. Graphene, particularly in its GO and rGO forms, exhibits outstanding qualities like high surface area, strong mechanical properties, and efficient thermal conductivity. Nevertheless, its hydrophobic characteristics, poor dispersion in water solutions, and potential toxicity limit its practical application. Chemical modifications, including functionalizing graphene with carbohydrate-based polymers like chitosan and hyaluronic acid, enhance graphene's dispersion, stability, and biocompatibility. Introducing functional groups facilitates interactions with these polymers, enabling pH-sensitive drug release for tumor targeting, as acidic environments can trigger the release of therapeutic agents. The positively charged amino groups in chitosan enhance drug loading and foster electrostatic interactions with negatively charged entities like siRNA or small molecule drugs, while hyaluronic acid exclusively binds to CD44 receptors on cancer cells, facilitating targeted drug delivery and reducing off-target effects. These carbohydrate polymers improve biocompatibility, reducing the chances of immune reaction and extending the circulation time of graphene-based nanocomposites in the blood, thus enabling more effective targeting of tumor sites. The chemistry of graphene composites modified with carbohydrate polymers is essential for improving the effectiveness of PTT and PDT, both of which are gaining importance in cancer therapy. Graphene, especially when reduced, exhibits excellent photothermal properties under NIR exposure, leading to localized heat generation that can destroy cancer cells. Altering graphene with carbohydrate polymers improves the biocompatibility of the composites and allows for specific targeting, thus enhancing therapeutic effectiveness while minimizing damage to healthy tissues. The ability of hyaluronic acid to attach to cancer-specific CD44 receptors ensures that the graphene composite preferentially gathers in tumor sites, improving the effectiveness of PTT. The functionalization of graphene with sugars like dextran and alginate enhances drug-loading capacity, enables controlled drug release in response to environmental factors, and reduces toxicity through gradual therapeutic release. These modifications create multifunctional nanocomposites for drug delivery, gene therapy, imaging, and phototherapy, improving targeted, personalized cancer treatments. By utilizing graphene's unique chemical properties, these composites address traditional cancer therapy limitations, enhancing effectiveness and safety.

CRediT authorship contribution statement

Zhenwang Zhang: Writing – review & editing, Writing – original draft, Methodology, Investigation. **Jinxiang Wang:** Writing – review & editing, Writing – original draft. **Lingmi Hou:** Writing – review & editing, Writing – original draft, Software, Resources. **Dan Zhu:** Writing – review & editing, Writing – original draft, Conceptualization. **Hai-Juan Xiao:** Writing – review & editing, Writing – original draft, Conceptualization. **Kaili Wang:** Writing – review & editing, Writing – original draft, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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