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Graphene Oxide: A Potential Drug Carrier for Cancer Therapy—Review

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Abstract

Graphene oxide (GO) is a single or few layer's sheet derived from graphite using strong oxidizing agents. Graphene oxide possesses outstanding aqueous processability, amphiphilicity, functionalizability, surface enhanced area and fluorescence ability. Hydrophilicity is an important property for mixing the material with ceramic or polymer matrixes while trying to improve their electrical and mechanical properties. Acquiring a promising application in the biomedical area, graphene molecules undergo complex interactions with the biological system, resulting in toxicity of the molecule. However, various approaches to overcome these problems have been established involving graphene modification, leading to the emerging role for graphene oxide, highly-tailored multifunctional targeted delivery vehicles of therapeutic agents to cancer cells or tissues due to its enhanced tissue penetration and cellular uptake both in vitro and in vivo. This review covers graphene oxide properties, functionalization, cytotoxicity and recent potential research studies on GO application in cancer therapy for the past 5 years (2013–2017).

Keywords: *Graphene oxide, functionalization, targeted delivery, cancer therapy*

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INTRODUCTION

Graphene was discovered by Geim and coworkers in 2004 who were credited with a Noble prize in physics [1, 2]. It is a novel one-atom-thick two-dimensional graphitic carbon system with interesting physical and chemical properties such as high electrical and thermal conductivity, mechanical strength and optical absorption properties [3–5]. The strong capacity of light absorption of nano-particles extends the absorption of visible light and near infrared ray in PTA (photothermal ablation therapy). This property of nano metallic material can induce protein degeneration and kill the tumor cells by localized heating [6–10].

Graphene's ability to interact with various biomolecules which can be used in drug and gene delivery, biosensing and tissue engineering, is due to the presence of delocalized p electrons and high surface area [11–16]. Graphene has a large aromatic surface and with more reactive edges. The surface area of graphene (2600 $m^2 g^{-1}$) is four magnitudes higher than the surface of any other nanomaterials explored for drug delivery. Due to monolayer structure of graphene, each atom is exposed on its surface. Therefore, it shows higher drug loading capacity than other nanomaterials [1, 17]. With the presence of optimized functional groups and high specific surface area, graphene has attracted great attention for biomedical applications [11, 18]. However, graphene molecules are not completely safe owing to complex interactions with solutes, proteins or cellular systems within the body and these interactions impact significantly on the behaviour or toxicity of the molecule; therefore, prior to these biological applications, several prerequisites should be undertaken. Initially, rational functionalization chemistry is inevitable to impart graphene with aqueous solubility and biocompatibility by formation of derivatives of graphene oxide [5].

Graphene oxide (GO), an oxidized form of grapheme (graphite) is synthesized using the Hummers method [19, 20]. It contains carboxylic acid, epoxide, and hydroxyl groups on its surface making it more hydrophilic and dispensable in water. The abundant functional

groups on its surface offer a variety of active sites for conjunction of organic small molecules, polymers, biomacromolecules and many other functional groups [20–22]. They can couple with some specific antibodies and ligands, which make multi-functional nanoparticles possibly improving the drug loading and delivery efficiency [23, 24]. GO and its chemically converted derivatives form stable suspensions in pure water however, have a tendency aggregate in salt or other biological solutions [11, 25]. Graphene sheets with suitable sizes are desired with size control on various length scales to interact suitably with living systems *in vitro* and *in vivo.*

Functionalization of Graphene Oxide

To modify the physical and chemical properties, GO functionalization can occur via both covalent and noncovalent mechanisms [26]. Covalent modifications involve chemical derivatives of GO produced by conjugation of hydrophilic polymers or nucleic acids (NAs), amine coupling to carboxylic groups, sulfonylation, or reactive intermediates such as radicals, nitrenes, carbenes, and arynes [27, 28]. This method changes the hybridization of sp2 carbon atoms of the p network into a sp3 configuration. In comparison, noncovalent modifications consist of van der Wals forces, electrostatic interactions, hydrogen bonding, and p-p stacking interactions. It does not affect the native structure and p-network of graphene, allowing the adsorption of hydrophobic molecules by a very high loading capacity and via p-stacking on both sides of the graphene surfaces [24, 29].

Many different graphene based materials have been developed by polymeric modification and conjugation strategies enhancing *in vivo* biocompatibility and circulation times of graphene oxide [30]. These strategies invoke monovalent interactions and conjugation with polymers to provide reactive species such as hydroxyls and amines, on their surfaces. Additionally further functionalization with targeting ligands can improve delivery specificity to cancer cells [24, 31].

Graphene Oxide Cytotoxicity

It has been well established above, of GOs great potential in the biomedical area. However, cytotoxicity remains a great concern. Several factors are involved in influencing cytotoxicity: charge, concentration, surface structure, lateral dimension, impurities, corona effect, and functionalization [32–36]. The cytotoxic effects of GO include the following: DNA and mitochondrial damage [32], inflammatory responses [37], autophagy [38], necrosis [39], apoptosis [40], and reactive oxygen species production that causes oxidative stress, the first step in ageing carcinogenesis, and mutagenesis mechanisms [36, 41]. These cytotoxic effects can result in non-biocompatible delivery systems. To reduce their cytotoxicity, obtain and understand unique properties of GO, chemical functionalization strategy was introduced.

Prevention and Reduction of Cytotoxic Effects of Graphene Oxide

Studies have confirmed that surface functionalization of GO with polymeric molecules commonly including as PEG, chitosan, dextran, pluronic, gelatin, and polyacrylic acid (PAA) and, hyaluronic acid remains an outstanding strategy for reducing cytotoxic impacts [42, 43].

PEG Functionalization

The first ever successful graphene based drug delivery system was formulated by functionalizing GO sheets with PEG. PEGylated GO showed low toxicity and excellent stability in physiological solutions including serum [44, 45]. PEG effectively decreased GO-induced acute tissue injuries, reduced GO aggregation and retention in the lungs, liver, and spleen facilitating GO organ clearance [46]. *In vitro* cytotoxicity study of pEGylated GO on breast cancer cell lines (EMT6) revealed that cell viability remained above 95% even at concentration up to 100 ug/ml^{-1} [47]. No significant proinflammatory cytokine secretion was found after treatment with GO-PEG [48]. Other chemotherapy drugs such as paclitaxel loaded on GO-PEG via p-p stacking and hydrophobic interactions showed an interesting anticancer effect on lung and breast cancers resulting in 66 to 90% tumor growth inhibition [49], prolonged blood circulation, high efficacy in tumor-targeting and suppressing [50]. However, PEG is a large and expensive

molecule with low biodegradability which may potentially increase GO bioaccumulation [45]. Another systemic study was performed to evaluate long-term toxicity of intravenously injected GO-PEG at a remarkable dose of 20 mg^2 kg^{-1} to mice. The results showed no noticeable organ damage or inflammation suggesting no obvious toxicity caused by intravenous injected GO-PEG at the tested dose [42].

Chitosan

Chitosan (CS) has proved to be a potential polymer in overcoming hemolytic property of GO in red blood cells caused by interactions of negatively charged GO with positively charged phosphatidylcholine lipids on the RBC outer membrane. Chitosan almost eliminates GO haemolytic activity through reducing the contact between GO and RBCs [51, 52]. *In vitro* cell toxicity assay with GO-CS showed no obvious cytotoxicity on HepG2 and Hella cells [53].

Dextran

Cytotoxicity of dextran modified GO (GO-DEX) versus pristine GO was evaluated on MCF-7 and 4T1 cells with different concentrations of GODEX and GO. Slight reductions of cell viability only were observed at very high concentration of GO-DEX (300 $lgml^{-1}$). However, uncoated GO showed high cytotoxicity even at low concentrations [54]. In another study, GO-DEX showed accumulation in the reticulo-endothelial system (RES) including spleen and liver after intravenous injection (IV); however within a week, the GO-DEX revealed obvious clearance from the mouse body. In comparison with GO, that was trapped in the lungs entirely, following IV and showed obvious pulmonary toxicity [55].

Polyacrylic Acid

Polyacrylic acid-graphene nano sheets (PAA-GNSs) demonstrated high aqueous solubility and stability in physiological solutions. PAA-GNSs could adsorb aromatic, water insoluble drugs and show strong pH-dependent behavior and efficient controlled release [56]. A comparative toxicity of several GO materials such as aminated GO (GO-NH2), poly (acrylic acid)-modified GO (GO-PAA), poly (acrylamide)-modified GO (GO-PAM), and PEGylated GO was conducted; results showed that functionalization with PEG and poly acrylic acid (PAA) induced less toxicity than others owing to their low protein adsorption in serum and weak interaction with macrophage. Toxicity to major organs was examined. The results revealed that GO-PAA-treated mice had the least impairment in lung and liver, compared to uncoated GO and other GO materials [57].

Gelatin

It is a well-established natural, nontoxic, and inexpensive polymer obtained by hydrolysis of collagen which is highly biocompatible and biodegradable with low immunogenicity. This reduces toxicity of gelatin-conjugated graphene [58, 59]. US-FDA classifies gelatin as a safe polymer) [60]. Gelatin acts as a capping agent for stabilizing graphene. Biocompatible gelatin-GNS demonstrated excellent dispensability and stability in distilled water and other various physiological solutions. Gelatin-graphene nanosheets were employed as carriers to be loaded with anticancer drugs for enhanced cellular uptake and drug delivery [61]. Cellular toxicity tests suggested that the gelatine-GNS conjugate was nontoxic for MCF-7 cells, even at concentration as high as 200 $mgml^{-1}$. The doxorubicin/gelatine-GNS composite exhibited high toxicity against MCF-7 cells and a gelatin-mediated sustained release *in vitro*. In addition, no clear cytotoxicity was found for gelatins modified GO against A549 cells even at high concentration up to 300 $mgml^{-1}$ [62].

Pluronic

pluronic F127-functionalized graphene was found to be effective in encapsulating doxorubicin (DOX) with high drug-loading efficiency. The presence of PF127 gave the graphene nanosheet high aqueous solubility and stability in physiological environment. It also showed pH-responsive drug release behaviour [63].

Chitosan

(CS) is a stimulus-responsive polymer with reversibly adjustable solubility by changing the pH value. CS can increase the cellular permeability and bioavailability of orally administered bioactives including proteins, peptides, oligonucleotides, and plasmids due to its g7F muco-adhesive properties [64, 65]. CS has positive charge which could also improve the cellular uptake of GO-CS-

camptothecin via electrostatic interactions with the negatively charged cell membrane. The GO-CS-CPT demonstrated potency with an IC_{50} of 29 um, while free CPT showed only a 20% growth inhibition with about the same concentration. Therefore, GO-functionalized chitosan can improve drug efficacy without increasing the chemotherapeutic drug dose and it showed remarkably high cytotoxicity in HepG2 and HeLa cell lines [66]. Notably, the loading capacity of GO-CS varies for different drugs, depending on the chemical structure and interactions of each drug with GO-CS. For example, drug loading ratio of ibuprophen (IBU) on GO-CS sheets was 0.097 $mgmg^{-1}$ and higher than 5-fluorouracil (5FU) (0.053 $mgmg^{-1}$) [67].

Hyaluronic Acid

Finally, *in vivo* toxicity studies showed that the resulting GO functionalized hyaluronic acid (HA) exhibited very low cytotoxicity, good blood compatibility, and no evident toxic effects in mice at a high exposure level of 10 mg kg^{-1} and at an exposure time of up to10 days [68].

Logically, it is can concluded that well-designed surface functionalization of GO can effectively decrease both its *in vitro* and *in vivo* toxicity making investigation and optimization of this platform important for discovery of ideal delivery system for *in vivo* cancer management.

CONVENTIONAL CANCER THERAPY

Cancer stands out as one of the major human diseases affecting different parts of the body. Cancerous tissues exhibit irregular growth leading to angiogenesis. This phenomenon is as a result of various signals from cancerous tissues and genetic mutations [69]. Conventional cancer therapies include three major approaches: chemotherapy, radiotherapy and surgery; all of which encounter challenges like poor bioavailability and intrinsic toxicity. Although they have exhibited a great deal of success, there are cytotoxic effects on normal cells; which is undesirable [70]. The development of novel nanomaterials like graphene and its derivatives could address these limitations [71–73]. Generally, graphene derived nanomaterials can be accumulated at higher concentration in tumor site compared to conventional drugs through enhanced permeability and retention (EPR) effect [69].

GRAPHENE OXIDE CARRIER MEDIATED TARGETED DELIVERY IN ANTICANCER THERAPY

Graphene oxide (GO) based targeted drug carrier is becoming of potential interest in the management of cancer. This is due to its selectivity characteristic for tumor cells greatly enhancing the delivery of anticancer drugs and their therapeutic value, while simultaneously reducing associated side effects. Understanding of the entry mechanism of graphene derivatives into cells is important for evaluation of its interaction with cells on its translation into clinic application. Endocytosis, an energy dependent mechanism is known to be the entry mechanism of graphene. Studies have suggested that due to the planar 2D structure, GO could be taken up by cancer cells via clathrin-mediated endocytosis [74, 75].

Recent Research Studies for the Past 5 years on Application of GO as a Carrier in Cancer Therapy

A number of studies on the use of graphene oxide in delivery of anticancer drugs have been reported on various cancer types. Below is a summary of recent reports on graphene mediated cancer treatment.

Liu *et al*. evaluated and reported transferrin modified graphene oxide for glioma-targeted drug delivery. Transferrin (Tf) is an iron-transporting serum glycoprotein that binds to receptors over-expressed at the surface of glioma cells, chosen as the ligand to develop Tf-conjugated PEGylated nanoscaled graphene oxide (GO) for loading and glioma targeting delivery of anticancer drug doxorubicin (Dox) (Tf-PEG-GO-Dox). Tf-GO with lateral dimensions of 100–400 nm exhibited a Dox loading ratio up to 115.4%. Compared with Dox-loaded PEGylated GO (PEG-GO-Dox) and free Dox, Tf-PEG-GO-Dox displayed greater intracellular delivery efficiency and stronger cytotoxicity against C6 glioma cells. A competition test showed that Tf was essential to glioma targeting *in vitro.*

According to HPLC assay, Tf-PEG-GO-Dox was capable of delivering more Dox into tumor *in vivo*. This was demonstrated by the Dox concentration in tumor tissue and also by contrapart tissue of the brain. There was significant life span extension in tumor bearing rats following administration of Tf-PEG-GO-Dox in comparison to the saline, Dox, and PEG-GO-Dox. It can be concluded, that they developed Tf-PEG-GO-Dox which exhibited significantly improved therapeutic efficacy for glioma both *in vitro* and *in vivo* [76].

In 2014, Song et al researched on hyaluronic acid-decorated graphene oxide nanohybrids as nanocarriers for targeted and pH-responsive anticancer drug delivery [77]. In this study, a novel nanohybrid of hyaluronic acid (HA)-decorated graphene oxide (GO) was fabricated as a targeted and pH-responsive drug delivery system for controlling the release of anticancer drug doxorubicin (DOX) for tumor therapy. For the preparation, DOX was first loaded onto GO nanocarriers via π-π stacking and hydrogen-bonding interactions, and then it was decorated with HA to produce HA-GO-DOX nanohybrids via H-bonding interactions. In this strategy, HA served as both, a targeting moiety and a hydrophilic group, making the as-prepared nanohybrids targeting stable and disperse. A high loading efficiency (42.9%) of DOX on the nanohybrids was also obtained. Cumulative DOX release from HA-GO-DOX was faster in pH 5.3 phosphate-buffered saline solution than that in pH 7.4, providing the basis for pH-response DOX release in the slightly acidic environment of tumor cells, while the much-slower DOX release from HA-GO-DOX than DOX showed the sustained drug-release capability of the nanohybrids. Fluorescent images of cellular uptake and cell viability analysis studies illustrated that these HA-GO-DOX nanohybrids significantly enhanced DOX accumulation in HA-targeted HepG2 cancer cells compared to HA-nontargeted RBMEC cells and subsequently induced selective cytotoxicity to HepG2 cells. *In vivo* antitumor efficiency of HA-GO-DOX nanohybrids in H22 hepatic cancer cell-bearing mice demonstrated increased tumor inhibition in comparison with free DOX and the GO-DOX formulations. They concluded that the HA-GO-DOX nanohybrids possess promising applications for delivery of anticancer drugs [77].

Zhong-Jun and colleagues in 2015 researched on functionalized nano-graphene oxide particles for targeted fluorescence imaging and photothermy of glioma U251 cells [6].

Functionalized nano-graphene oxide (nano-GO) particles were formulated; then, using U251 glioma cells, they observed targeted fluorescence imaging and photothermy under near infrared (NIR) exposure. The functionalized nano-GO-Tf-FITC particles were prepared and then were incubated with U251 glioma cells. Estimation of CCK8 cell activity was adopted for measurement of cytotoxicity. The effect of fluorescence in imaging was detected by fluorescence microscope with anti-CD71-FITC as a control. Finally, we detected the killing efficacy with flow cytometry after an 808 nm NIR exposure. It was observed that both nano-GO-Tf-FITC group and CD71-FITC group exhibited green-yellow fluorescence, while the control group without the target molecule nano-GO-FITC was negative. There is no significant difference between the nano-GO-FITC groups and control group. In addition, the apoptosis and death index of nano-GO-Tf-FITC group was significantly higher than that of nano-GO-FITC and blank control group ($P<0.05$). So, it can be concluded that the nano-GO-Tf-FITC particles with good biological compatibility and low cytotoxicity are successfully made, which have an observed effect of target imaging and photothermal therapy on glioma U251 cells. A new functionalized nano-GO-Tf-FITC particle was successfully prepared with Tf as a targeted ligand and FITC which is soluble in water and has a strong binding force with protein as a fluorescence indicator based on the special property of photothermal conversion of GO. The particles could have a targeted combination with glioma cells for fluorescent imaging of tumor cells and significantly kill the tumor cells with targeted photothermy under an 808 nm near infrared laser exposure, thus laying a foundation for further researches on the glioma U251 cells targeted fluorescence imaging and photothermy [6].

Ma *et al*. in 2017 studied folic acid-grafted bovine serum albumin decorated graphene oxide: An efficient drug carrier for targeted cancer therapy [78]. Direct grafting of target molecules on GO usually results in aggregation of physiological fluid, limiting its biomedical applications. Here, Ma *et al.* proposed a new strategy to construct targeting GO drug carrier using folic acid grafted bovine serum albumin (FA-BSA) as both, the stabilizer and targeting agent. FA-BSA decorated graphene oxide-based nanocomposite (FA-BSA/GO) was fabricated by the physical adsorption of FA-BSA on GO, which was developed as a targeting drug delivery carrier. FA-BSA/GO as the drug carrier was associated with anticancer drug doxorubicin (DOX) through π-π and hydrogen-bond interactions, resulting in high drug loading (up to 437.43 μg DOX/mgFA-BSA/GO). FA-BSA/GO/DOX systems demonstrated pH responsive and sustained drug release. The hemolysis ratio of FA-BSA/GO was less than 5%. The results of this study confirmed the potential for fabrication of highly stable and dispersible GO-based targeting delivery systems for efficient cancer therapy [78].

Kim and Michael evaluated and reported neutron-activatable radionuclide for chemotherapy using graphene oxide nanoplatelets [79]. Neutron-activation can be defined as potential process that involves radiotherapeutics generation with reduced handling of radioactive materials. Grapheme oxide nanoplatelets (GONs) were examined as a carrier for neutron-activatable holmium with the purpose of exploiting inherent characteristics for theranostic application. GONs were hypothesized to be an ideal candidate for this application owing to their desirable characteristics such as a rigid structure, high metal loading capacity, low density, heat resistance, and the ability to withstand harsh environments associated with the neutron-activation process. Increased dispersibility and biocompatibility was observed by non-covalently PEGylated GONs (GONs-PEG) along with enhanced holmium loading capacity about two-fold than that of GONs, following neutron irradiation. The *in vitro* cell-based cytotoxicity analysis of GONs-based formulations with non-radioactive holmium confirmed their safety profile within cells. The results demonstrated the potential of GONs as a carrier of neutron-activatable radio therapeutic agents [79].

Ya-Shu *et al.* studied targeted delivery of chemotherapy drugs using magnetic graphene oxide as a nanocarrier [80]. Magnetic targeted functionalized graphene oxide (GO) complex was formulated as a nanocarrier with pH-susceptible controlled release of drugs to tumour cells. Magnetic graphene oxide (mGO) was prepared by chemical co-precipitation of Fe3O4 magnetic nanoparticles on GO nano-platelets. The mGO was successively modified by chitosan and mPEG-NHS through covalent bindings to synthesize mGOC-PEG. The polyethylene glycol (PEG) moiety is expected to prolong the circulation time of mGO by reducing the reticuloendothelial system clearance. Irinotecan (CPT-11) or doxorubicin (DOX) was loaded to mGOC-PEG through π-π stacking interactions for magnetic targeted delivery of the cancer chemotherapy drug. The best values of loading efficiency and loading content of CPT-11 were 54 and 2.7% respectively; whereas for DOX, they were 65 and 393%. The pH-dependent drug release profile was further experimented at different pHs, in which ~60% of DOX was released at pH 5.4 and ~10% was released at pH 7.4. In contrast, ~90% CPT-11 was released at pH 5.4 and ~70% at pH 7.4. Based on the drug loading and release characteristics, mGOC-PEG/DOX was further chosen for *in vitro* cytotoxicity tests against U87 human glioblastoma cell line. The IC50 value of mGOC-PEG/DOX was found to be similar to that of free DOX but was reduced dramatically when subjected to magnetic targeting. They therefore concluded that with the high drug loading and pH-dependent drug release properties, mGOC-PEG will be a promising drug carrier for targeted delivery of chemotherapy drugs in cancer therapy [80].

And finally, in an interesting turn of events a novel and potential property of graphene oxide has recently been highlighted in the Hindu newspaper on June 25, 2017 [81]. This happened in a serendipitous discovery by a team of researchers at the Indian Institute of

Science Education and Research (IISER), Pune. Serendipitously they found that when cisplatin an FDA-approved anticancer drug was added, the graphene oxide sheets self-assembled into spherical nanoparticles enclosing the drug within. This kind of shape-shifting transformation of the graphene oxide sheets into a spherical structure mechanism is under exploration, it was suggested that the drug is reacting with graphene oxide and transforming the graphene sheet into a ball-like structure, a kind of 'molecular stitching.

Additionally, proflavine and doxorubicin DNA-damaging anticancer drugs that bind to graphene oxide through non-covalent bond were used too. These two drugs have no role in changing the morphology of graphene oxide from a sheet to a spherical nanoparticle. The formed nanoparticles of size 90–120 nm containing cisplatin and either of the two anticancer drugs were taken up by cervical cancer cells leading to programmed cell death. By the drug's action of binding to the DNA strands and breaking the strands, the cell division is disrupted resulting into apoptosis.

Resuming Shape

Graphene oxide formed spheres delivered the drug to the cervical cancer cells intriguingly, when cisplatin was released inside the cell, the spherical nanoparticle lost its shape and once more regained its original sheet-like structure. This was confirmed using scanning electron-microscopy.

The nanoparticle containing cisplatin alone was able to kill cancer cells. But there is additive effect when two drugs are used together and efficiency of killing the cancer cells becomes better.

The cisplatin nanoparticles containing either proflavine (is still undergoing animal trials) or doxorubicin, were found to get into the lysosomes of a cell in a time-dependent manner. Once inside the lysosomes, the drugs were released in a slow and sustained manner and killed the cancer cells predominantly through programmed cell death. In the case cisplatin nanoparticles containing proflavine, about 54% of proflavine was released in about 2 days while 22% of cisplatin was released after 3 days. For cisplatin nanoparticles containing doxorubicin, more (33%) of cisplatin and less (22%) of doxorubicin were released after 3 days. Slow release of the drugs is better as the drugs will be effective for a longer period of time.

The nanoparticles containing the drugs targeted only the cancer cells. Though the study found that comparable concentration of doxorubicin and proflavine was required to kill 50% of the cells at the end of 48 h. It can be concluded that Nandi and colleagues successfully developed a novel cancer drug delivery system using graphene oxide nanoparticles. A cisplatin-induced self-assembly of graphene oxide sheets into spherical nanoparticles for damaging sub-cellular DNA to programmed cell death [82].

CONCLUSION AND FUTURE PROSPECTS

Graphene oxide is a cheaply abundant carbon-based material, which can be used for various applications ranging from material science to biomedical research. From the abounding literature on the application of graphene oxide in the biomedical field specifically cancer therapy, it can be seen that GO has dual action potential in chemotherapy but also phototherapy as the nano GO sheets are found to possess photo-luminescent activity in the visible and infrared regions. This intrinsic photoluminescence (PL) of nano GO can be used for live cell imaging with little background in the near-infrared (NIR). GO is the next hope for potential therapeutic carriers of anticancer drugs and radionuclides too owing to the novel graphitic nanostructures, combined with multi-functionalities, its biocompatibility, photoluminescence, drug high loading, controlled release-targeted delivery, with minimized side effects.

In the near future, there is desperate need for researchers to undertake massive studies using a variety of cancer cells and eventually animal models, especially targeting the mitochondria (power house of cells). It can be anticipated therefore that graphene oxide-based nanoplatform will be useful for next-generation cancer therapy.

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