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Functional Modifications of Graphene Oxide: A Practical and Reliable Choice for Enhanced Photodynamic Therapy in Cancer

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Abstract

Introduction: Photodynamic therapy (PDT) has emerged as a minimally invasive strategy for cancer treatment because of its spatial selectivity and relatively low systemic toxicity. However, its clinical efficacy is limited by poor solubility and nonspecific distribution of photosensitizers (PSs), rapid degradation, and tumor hypoxia. Recently, graphene oxide (GO) and its derivatives have gained considerable attention as multifunctional nanocarriers capable of overcoming these limitations.

Methods: A comprehensive literature review was conducted using recent studies focused on GO based nanoplatforms for PDT applications in cancer therapy. Relevant articles were analyzed to evaluate the physicochemical properties of GO, photosensitizer loading mechanisms, surface functionalization approaches, and therapeutic performance in different therapeutic strategies.

Results: The reviewed studies demonstrated that GO possesses unique physicochemical characteristics enabling efficient loading of PS molecules through π–π interactions and other surface modification strategies. Functionalization approaches, including polymer coating, targeting ligands, metal nanoparticle incorporation, and stimuli responsive systems, improved PS stability, tumor targeting, and reactive oxygen species (ROS) generation. Furthermore, GO based systems showed promising performance in combined photodynamic and photothermal therapy (PDT/PTT), resulting in synergistic anticancer effects and improved therapeutic efficacy.

Conclusion: Overall, GO based nanoplatforms represent a promising strategy for improving the therapeutic efficiency, targeting capability, and multifunctionality of PDT based cancer treatments. Nevertheless, further investigations regarding long term biosafety and clinical translation are still required.

Keywords: Graphene oxide, Photodynamic therapy, Photosensitizers, Reactive oxygen species, Nanomedicine, Cancer therapy

Introduction

Cancer remains a major global health burden, driving interest in safer therapies such as photodynamic therapy (PDT), which induces ROS-mediated tumor death with high selectivity.[1] Yet PDT efficacy is hindered by poor photosensitizer solubility, low bioavailability, non-specific distribution, limited light penetration, and tumor hypoxia, along with resistance mechanisms reducing ROS generation.[2]

Graphene oxide (GO) offers a versatile nanoplatform with high loading capacity, abundant functional groups, and intrinsic photothermal activity, improving photosensitizer delivery and enabling synergistic PDT–PTT or chemo-PDT approaches.[1,3] Surface engineering—PEGylation, targeting ligands, and stimuli-responsive elements—further enhances tumor targeting and therapeutic efficiency.

However, concerns regarding biosafety, long-term toxicity, synthesis reproducibility, and translational gaps remain obstacles to clinical application.[4–6]

This review outlines key GO-based strategies to improve PDT efficacy and highlights remaining challenges in advancing GO theranostics for future cancer therapy.

Graphene Oxide in Cancer Therapy

Graphene oxide (GO) is produced by introducing oxygen-containing groups (hydroxyl, carboxyl, epoxide) onto graphene sheets, improving aqueous dispersibility and enabling covalent or noncovalent functionalization. Its large surface area (~2630 m^2 g^{-1}) allows efficient

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π–π interactions with aromatic drugs, including photosensitizers, enhancing loading capacity and delivery stability.[7]

GO protects photosensitizers such as phthalocyanines and porphyrins from degradation and enables stimuli-responsive release (pH, enzymes, light), while ligand conjugation (e.g., folic acid, RGD peptides) improves tumor targeting. Passive accumulation occurs through the EPR effect, with cellular uptake mainly via endocytosis; physicochemical features such as oxidation degree, size, thickness, and surface charge influence biodistribution and clearance.[8–10] GO also supports synergistic PDT–PTT therapy.

However, unmodified GO may cause inflammation, oxidative stress, hemolysis, and aggregation, with concerns about long-term toxicity and accumulation in organs. Surface engineering strategies, including PEGylation, polymer coatings, and size control, improve biocompatibility and systemic clearance.[11,12]

PDT Mechanism in Cancer Therapy

Photodynamic therapy (PDT) uses light-activated photosensitizers to generate cytotoxic ROS that induce tumor cell death. Upon light excitation, the photosensitizer transitions from the singlet to triplet state and produces ROS through Type I (radical formation) or Type II reactions that generate singlet oxygen ($^1O_2$), the main mediator of PDT cytotoxicity.[11,13]

Although photosensitizers such as porphyrins, chlorins, and phthalocyanines show therapeutic potential, their clinical use is limited by poor solubility, aggregation-induced quenching, limited tumor selectivity, photobleaching, and insufficient tumor penetration, which reduce ROS generation and therapeutic efficacy. [14]

Graphene oxide (GO), a two-dimensional carbon nanomaterial with high surface area and abundant functional groups, enhances photosensitizer loading through π–π interactions, improving stability, dispersion, and photodynamic efficiency.[15,16] GO nanocomposites can also enable stimuli-responsive release (pH, enzymes, or light) and ligand-mediated tumor targeting, increasing delivery precision and cellular uptake.[17] Moreover, the intrinsic photothermal conversion of GO allows synergistic PDT–PTT therapy, enhancing ROS production and antitumor efficacy.[18]

Improving PDT Through Surface Modifications of GO

Functionalization of GO with Photosensitizers (GO-PS Conjugates)

Graphene oxide (GO) serves as an effective nanocarrier for various photosensitizers owing to its large surface area, abundant surface functional groups (–COOH, –OH, and epoxy), and versatile binding mechanisms, including non-covalent π–π stacking, electrostatic interactions, and covalent bonding. These interactions help prevent aggregation-induced quenching of PS molecules and improve their photophysical stability. Consequently, GO–PS hybrid systems exhibit enhanced water solubility, photostability, ROS generation, and improved tumor targeting, as GO promotes better dispersion and bioavailability of PSs at the tumor site.

Porphyrins

Porphyrin-based photosensitizers are widely used in PDT due to strong absorption in the Soret (~400 nm) and Q (600–700 nm) bands, enabling efficient ROS generation. Conjugation with GO or rGO enhances photostability, tumor targeting, and ROS yield through π–π stacking, with rGO providing stronger binding and higher loading efficiency due to its greater sp^2 carbon content. Representative porphyrins investigated in GO/rGO-based systems include HpD, Photofrin, PpIX, TCPP, and TMPyP.[19]

HpD interacts with GO mainly via π–π stacking, which stabilizes molecules, reduces aggregation, and enhances cellular uptake.[20] Photofrin, derived from HpD, benefits from GO conjugation through improved solubility, increased ROS yield, and prolonged photostability.[1] rGO–PpIX nanohybrids, formed via covalent or electrostatic interactions, significantly enhance ROS production and apoptosis under 635 nm irradiation.[21] TCPP binds strongly to GO via hydrogen bonding and electrostatic interactions through its carboxyl groups, improving PDT performance and surface anchoring stability.[22] TMPyP and sulfonated porphyrins adsorb non-covalently onto GO through π–π and electrostatic interactions, enhancing ROS generation and demonstrating notable antimicrobial and anticancer activity (Table 1).[23,24]

Phthalocyanines (PCs)

PCs are stable macrocyclic compounds with strong absorption in the NIR Q-band (~600–700 nm), making them highly suitable for deep-tissue PDT. They exhibit high photostability and efficient singlet oxygen ($^1O_2$) generation. However, in aqueous environments, they tend to aggregate, significantly lowering the ROS quantum yield (Table 2).[25]

(i) Cholesterol–ZnPc (Chol–ZnPc)

A ZnPc conjugated to GO through π–π stacking interactions and functionalized with cholesterol showed a prominent increase in singlet oxygen generation, with the quantum yield (Φ_Δ) rising from 0.54 to 0.78. Additionally, this composite exhibits an enhanced fluorescence quantum yield (Φ_F ≈ 0.36), resulting from reduced aggregation.[25]

(ii) ZnPc(NO_2)$_4$–GO

ZnPc(NO_2)$_4$–GO is a nanoparticle system in which nitro-substituted zinc phthalocyanine is conjugated to graphene oxide. This composite demonstrates an increase in singlet oxygen production from approximately 0.56 to 0.71.[26]

(iii) GO–NAM–ZnPc

GO–NAM–ZnPc is a multifunctional nanocomposite in

Table 1. Porphyrin–GO conjugates enhance PDT by increasing ROS generation, solubility, and cellular uptake. Porphyrins (HpD, Photofrin, PpIX, TCPP, TMPyP) bind GO via π–π or electrostatic interactions, yielding improved anticancer and antimicrobial activity.

Porphyrin type	Comments	[Ref]
HpD	• Main Features: Complex stabilization and enhanced cellular uptake. • Type of Interaction with GO/rGO: π–π stacking. • Applications: One of the first clinically used PSs.	20
Photofrin	• Main Features: Improved solubility and PDT efficiency. • Type of Interaction with GO/rGO: Non-covalent. • Applications: Clinically relevant first-generation mixture.	1
PpIX	• Main Features: Increased ROS production, apoptosis induction under 635 nm irradiation. • Type of Interaction with GO/rGO: Covalent or electrostatic. • Applications: Effective cancer therapy.	21
TCPP	• Main Features: Strong GO binding, enhanced PDT efficacy. • Type of Interaction with GO/rGO: Hydrogen bonding and electrostatic. • Applications: Improved therapeutic outcomes.	22
TMPyP	• Main Features: Boosted ROS generation under visible and NIR light. • Type of Interaction with GO/rGO: Electrostatic adsorption. • Applications: Potential antimicrobial and anticancer agent.	23
Sulfonated porphyrins	• Main Features: High solubility, efficient ROS generation. • Type of Interaction with GO/rGO: Electrostatic attachment. • Applications: Used in antimicrobial GO hybrids.	24

Table 2. Phthalocyanine-GO conjugates in PDT enhance treatment efficacy by improving PS dispersion, photostability, and ROS generation. Functionalization techniques, such as π–π stacking, PEGylation, and folic acid targeting, also enhance cellular uptake, water solubility, and tumor specificity. These nanohybrids are excellent platforms for both in vitro and in vivo applications in cancer phototherapy and antimicrobial uses.

Phthalocyanine type	Comments	[Ref]
Chol–ZnPc	• Type of Interaction with GO: π–π stacking. • Main Features: Φ_Δ ↑ (0.54 → 0.78), Φ_F ≈ 0.36. • Applications: Improved ROS generation.	25
$ZnPc(NO_2)_4$	• Type of Interaction with GO: π–π stacking. • Main Features: Φ_Δ ↑ (0.56 → 0.71). • Applications: Enhanced ROS, better dispersion.	26
NAM–ZnPc	• Type of Interaction with GO: Covalent + π–π. • Main Features: Enhanced uptake and ROS. • Applications: Antimicrobial and anticancer.	27
AlPc / GO–SiPc	• Type of Interaction with GO: Theoretical/ spectroscopic binding. • Main Features: Reduced recombination. • Applications: Photophysical enhancement for PDT.	25
ZnPc–PEG	• Type of Interaction with GO: PEGylation. • Main Features: ↑ Stability, ↓ Toxicity. • Applications: Prolonged circulation in vivo.	25
Tetracarboxy-ZnPc	• Type of Interaction with GO: Hydrogen bonding & electrostatic. • Main Features: ↑ Dispersion, ↑ PDT efficacy. • Applications: In vitro enhancement.	25
ZnPc–FA	• Type of Interaction with GO: Folic acid targeting. • Main Features: Targeted delivery, ↑ ROS. • Applications: Selective cancer therapy.	25

which zinc phthalocyanine is modified with nicotinamide (NAM) and immobilized onto GO. This system exhibits effective anticancer and antimicrobial PDT activity.[27]

(iv) GO–AlPc and GO–SiPc Conjugates

Aluminum and silicon phthalocyanines conjugated to GO were investigated using theoretical calculations and spectroscopic analyses to evaluate their photophysical properties, thereby increasing their PDT efficiency.[25]

(v) GO–ZnPc–PEG

PEGylation of GO–ZnPc significantly enhances colloidal stability, prolongs blood circulation time, and reduces systemic toxicity.[25]

(vi) Tetracarboxy-ZnPc–GO

Tetracarboxy-ZnPc molecules containing four carboxylic acid groups exhibit strong electrostatic and hydrogen-bonding interactions with GO.[25]

(vii) GO–ZnPc–FA

Functionalization of GO–ZnPc with folic acid enables selective uptake via folate receptor–mediated endocytosis in tumor cells.[25]

Chlorins

Chlorins, reduced porphyrin derivatives with strong NIR absorption (~660–670 nm), are well suited for deep-tumor PDT. Their π–π interaction with GO (Table 3) enhances

Table 3. Chlorin–GO conjugates, particularly with Ce6, show improved dispersion, photostability, ROS generation, and tumor targeting via π–π interactions. PEG, folic acid, or aptamer functionalization further enhances uptake and selectivity, with in vitro and in vivo studies confirming superior PDT efficacy and reduced off-target toxicity

Chlorin type	Comments	[Ref]
GO–PEG–Ce6 / FA–GO–Ce6	• Type of Interaction with GO/rGO: π–π stacking. • Functional Additives: PEG, Folic Acid. • Main Features: Enhanced ROS, fluorescence, & PA imaging. • Applications: Targeted cancer PDT.	8,29
FLG–Ce6	• Type of Interaction with GO/rGO: π–π stacking. • Functional Additives: - • Main Features: ~5 × ROS, strong antimicrobial effect. • Applications: Antifungal (Candida albicans).	30
GO–Ce6–FA / GO–Ce6–Aptamer	• Type of Interaction with GO/rGO: π–π stacking + targeting. • Functional Additives: Folic Acid, Aptamers. • Main Features: ~5 × ROS, strong antimicrobial effect. • Applications: In vivo tumor inhibition.	10

photodynamic performance (Table 3).[10,28]

use studies report higher therapeutic efficacy with reduced off-target toxicity.[10]

(i) Chlorin e6 (Ce6)

Ce6 is a key second-generation photosensitizer with strong NIR absorption. GO–Ce6 platforms improve tumor accumulation via EPR and ligand targeting, increase ROS efficiency, and enable dual fluorescence/photoacoustic imaging for tumor visualization.[8,29]

(ii) FLG–Ce6

FLG–Ce6 hybrids produce ~5 × higher ROS than free Ce6 and also show antimicrobial activity, including PDT inactivation of *Candida albicans*, suggesting applications beyond cancer therapy.[30]

(iii) Targeted GO–Ce6 Systems

GO–Ce6 functionalized with ligands (e.g., FA, aptamers) promotes receptor-mediated uptake, enhances intracellular Ce6 levels, boosts ROS at tumor sites, and improves PDT selectivity. In vivo mo

Phenothiazines

Phenothiazines such as methylene blue (MB) absorb red light (~660 nm) but suffer from aggregation, rapid clearance, and poor uptake. π–π conjugation with GO improves stability, intracellular delivery, ROS generation, and overall PDT efficacy.[31,32]

(i) GO–MB Nanocomposites

GO–MB systems achieve > 40% greater cancer cell killing than free MB at low doses due to enhanced singlet oxygen production and improved cellular delivery, overcoming MB's pharmacokinetic limitations.[33]

(ii) GO–MB with Pluronic F127

GO–MB–F127 hybrids provide synergistic photodynamic/photothermal effects, with Pluronic F127 enhancing dispersion and stability. Under NIR irradiation, combined ROS generation and GO-mediated hyperthermia significantly improve in vivo tumor eradication (Table 4).[34]

Rhodamines

Rhodamines are fluorescent photosensitizers used in imaging-guided PDT due to strong red emission, enabling simultaneous tumor visualization and activation. GO integration creates multifunctional theranostic platforms combining fluorescence imaging, PDT, and PTT (Table 5).[35]

(i) Rhodamine B–PEG–FA–GO

This platform integrates Rhodamine B (imaging/PDT), PEG (solubility and stability), FA (tumor targeting), and GO (carrier/PTT). In vivo studies in Ehrlich tumor-bearing mice show enhanced tumor accumulation and therapeutic efficacy through combined targeting, imaging, PDT, and PTT.[36]

(ii) GO–Rhodamine 123

GO–Rhodamine 123 hybrids improve fluorescence stability, enabling real-time monitoring of cellular uptake and intracellular transport in GO-based delivery studies.[37,38]

(iii) Rhodamine B–Loaded MSNs Conjugated with GO

Rhodamine B–loaded MSNs conjugated with GO enable controlled drug release and improved PDT, with enhanced photothermal response, drug retention, and antitumor activity.[39]

(iv) Rhodamine 123–Liposome–GO Hybrids

Liposomal GO–Rhodamine systems combine fluorescence imaging with PDT/PTT. Liposomes improve biocompatibility and uptake, while GO enhances ROS generation and photothermal conversion for multimodal cancer therapy with real-time monitoring.[35]

BODIPY

BODIPY fluorophores are highly stable, tunable photosensitizers widely used in imaging-guided PDT. Structural modifications enable NIR activation, deeper tissue penetration, and enhanced ROS generation,

making BODIPY derivatives strong candidates for phototheranostic applications.[40]

(i) Iodinated or NIR-Absorbing BODIPY–GO Nanodots

These nanodots generate ROS efficiently under visible/NIR light and deplete intracellular GSH, weakening tumor antioxidant defenses and producing potent PDT effects against resistant tumors.[41]

(ii) Mn (II)-Complexed BODIPY–GO Conjugates

Mn(II)-complexed BODIPY–GO systems act as H_2O_2-responsive, oxygen-producing nanoplatforms. By generating O_2 in situ, they relieve tumor hypoxia and significantly enhance PDT in oxygen-deficient microenvironments.[42]

(iii) Heavy Atom-Substituted BODIPY–GO Systems

Iodinated or brominated BODIPY analogues show enhanced intersystem crossing and singlet oxygen production. GO conjugation further boosts ROS yields and phototherapeutic performance through improved stabilization and cellular delivery.[43]

(iv) BODIPY-Based Nanoprobes Coupled with GO

BODIPY–GO nanoprobes provide multicolor fluorescence imaging combined with effective PDT, supporting precise tumor localization, real-time tracking, and integrated therapeutic functionality.[44]

(v) Hybrid BODIPY–Porphyrin Systems

BODIPY–porphyrin hybrids offer synergistic light harvesting and improved ROS generation. Preclinical studies report strong antitumor efficacy, positioning these dual-chromophore constructs as advanced next-generation PDT agents with translational potential (Table 6).[44]

Biocompatible Polymers (PEGylation, Chitosan, etc.)

Pristine graphene oxide (GO) can induce cytotoxicity, oxidative stress, and aggregation in physiological environments, which limits its biomedical applicability. Surface functionalization with biocompatible polymers such as polyethylene glycol (PEG) or chitosan markedly improves the stability and biosafety of GO-based systems.[1]

PEGylation, achieved through covalent or noncovalent attachment of PEG chains, enhances GO biocompatibility and pharmacokinetics by forming a hydrated steric barrier that reduces protein adsorption and MPS clearance. This prolonged circulation facilitates passive tumor accumulation via the EPR effect.[9,15] PEGylation also improves colloidal stability by preventing sheet aggregation through steric repulsion, thereby enhancing dispersibility

Table 4. GO conjugation significantly increases methylene blue photodynamic activity by increasing ROS production and site-directed targeting. Dual-mode platforms (PDT + PTT) further increase therapy to an even greater extent, representing a very promising roadmap for future cancer treatment.

Phenothiazines	Comments	[Ref]
GO–MB	• Type of Interaction with GO/rGO: π–π stacking, electrostatic forces. • Main Features: enhanced singlet oxygen generation, improved cellular uptake, >40% ↑ cancer cell cytotoxicity. • Application: PDT against cancer cells.	33
GO–MB + Pluronic F127	• Type of Interaction with GO/rGO: Nanohybrid formulation. • Main Features: Combined PDT/PTT, improved tumor eradication due to ROS + hyperthermia effects. • Application: In vivo anticancer therapy.	34

Table 5. Rhodamines are fluorescent photodynamic photosensitizers that enable simultaneous imaging and treatment of tumors. Their conjugation with GO enhances fluorescence stability, reduces ROS generation, and improves target delivery, thereby enhancing the efficacy of combined PDT and PTT.

Rhodamines	Main Features	Application	[Ref]
Rhodamine B–PEG–FA–GO	• Red fluorescence for tumor imaging. • Targeted delivery. • Combined PDT/PTT.	• Enhanced tumor accumulation and therapeutic efficacy in Ehrlich tumor-bearing mice.	36
Rhodamine 123–GO	• Strong binding affinity to GO. • Stable fluorescence.	• Real-time monitoring of cellular uptake and distribution.	37,38
Rhodamine B-loaded mesoporous silica NPs–GO	• Controlled drug release. • Multi-functional platform.	• Enhanced PDT efficacy with targeted tumor treatment.	39
Rhodamine 123–liposome–GO hybrids	• Effective cellular uptake monitoring. • Fluorescence imaging combined with PDT/PTT.	• Combined imaging and therapeutic application.	35

Table 6. GO–BODIPY conjugates form multifunctional nanoplatforms for imaging-guided PDT, enabling enhanced ROS generation, NIR activation, tumor microenvironment responsiveness, and fluorescence tracking, with strong potential for cancer theranostics.

BODIPY Type	Modification	Main Features	Application	[Ref]
Iodinated/NIR-absorbing BODIPY	GO Nanodots	Enhanced ROS generation and GSH depletion	Improved PDT efficacy under visible/NIR light	41
Mn(II)-complexed BODIPY	GO Nanodots	H_2O_2-responsive, oxygen generation	Enhanced PDT in hypoxic tumors	42
Heavy atom-substituted BODIPY (Br/I)	GO Nanodots	Increased intersystem crossing and $^1O_2$ yield	Improved phototoxicity and ROS production	43
BODIPY-based nanoprobes	GO Hybrids	Multicolor fluorescence imaging	theranostics with tumor tracking and PDT	44
BODIPY–Porphyrin Hybrids	GO Nanocomposites.	Combined photophysical advantages of both dyes	Enhanced light harvesting and ROS generation	44

and minimizing nonspecific cellular interactions.[45]

Chitosan, a biodegradable cationic polysaccharide, further enhances GO performance through strong electrostatic interactions with negatively charged membranes, increasing cellular uptake.[46] Chitosan-modified GO improves intracellular delivery, supports endosomal escape, and enables sustained release in gene or RNA delivery applications.[47] Its abundant amine ($-NH_2$) groups allow conjugation with photosensitizers, targeting ligands, drugs, and imaging probes, enabling multifunctional and stimuli-responsive GO nanoplatforms for cancer theranostics.[48]

Dual modification with PEG and chitosan integrates prolonged systemic circulation with enhanced cellular internalization, producing nanocarriers with improved pharmacokinetics, reduced toxicity, and increased tumor accumulation. Such hybrid GO systems have demonstrated promising results in chemo-phototherapy, PDT, and PTT, achieving enhanced therapeutic efficacy with minimized off-target effects (Figure 1).[49–51]

Ligand-Based Targeting (Folic Acid, RGD, Aptamers, Antibodies)

Ligand functionalization of graphene oxide (GO) enhances tumor targeting and receptor-mediated uptake by enabling selective binding to overexpressed cancer-associated receptors, thereby improving intracellular delivery and reducing off-target accumulation.

Folic acid (FA) is widely used due to folate receptor-α overexpression in many epithelial cancers. FA-conjugated GO facilitates selective cellular internalization and improves the delivery of photosensitizers and therapeutics, resulting in enhanced PDT efficacy through increased intracellular accumulation and improved endosomal escape.[52]

RGD peptides target integrin αvβ3 receptors that are highly expressed in angiogenic tumor vasculature and metastatic cells. GO–RGD nanocomposites demonstrate improved tumor homing, deeper tissue penetration, and enhanced cellular uptake, supporting their use in combined PDT/PTT and anti-angiogenic therapies.[53]

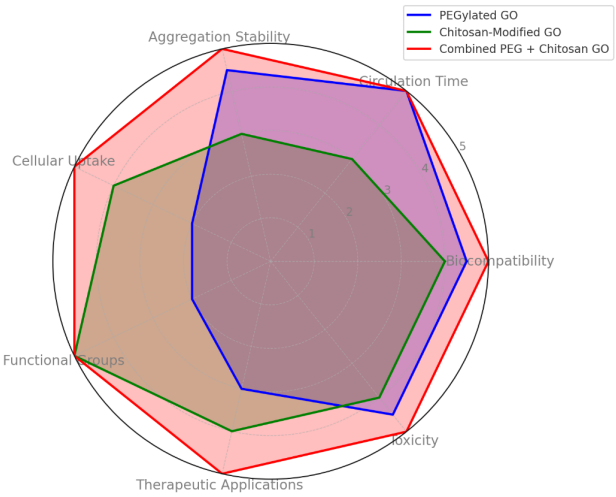


Figure 1. Radar plot comparing polymer-coated GO nanosystems. PEGylated GO improves circulation, biocompatibility, and colloidal stability, while chitosan-modified GO increases cellular uptake and offers abundant amine groups. A combined PEG–chitosan coating synergistically enhances stability, pharmacokinetics, tumor accumulation, and therapeutic efficacy with reduced systemic toxicity

Aptamers—single-stranded DNA or RNA molecules with defined three-dimensional structures—exhibit high affinity for tumor-associated biomarkers. GO–aptamer conjugates enable precise cargo delivery while reducing systemic toxicity, and their programmability supports theranostic platforms integrating imaging, PDT, and controlled drug release.[54]

Monoclonal antibodies (mAbs) provide the highest biological specificity among targeting ligands. Antibody-functionalized GO nanocarriers selectively recognize tumor-associated antigens, enabling targeted delivery, imaging, and enhanced photosensitizer accumulation. These systems may also activate immune pathways contributing to anticancer responses and have been applied in GO-based photodynamic and photothermal therapies as well as multimodal imaging platforms (Table 7).[55]

Metal and Magnetic Nanoparticles (AuNPs, Fe_3O_4, AgNPs)

Metallic and magnetic nanoparticles function as [multifunctional enhancers of GO-based photodynamic therapy (PDT)] due to their [unique optical, magnetic, and catalytic properties]. These nanomaterials improve light–tissue interactions, elevate reactive oxygen species (ROS) formation, and facilitate multimodal imaging and targeted delivery [Integration of AuNPs, Fe_3O_4, or AgNPs into GO-hybrid systems result in improved PS activation, enhanced photothermal conversion, and synergetic therapeutic outcomes] (Table 8).[56]

Gold Nanoparticles (AuNPs)

Gold nanoparticles (AuNPs) exhibit pronounced surface plasmon resonance (SPR), enabling strong absorption and scattering of visible and NIR light and concentrating electromagnetic energy at their surface, which enhances the excitation of conjugated photosensitizers (PSs). When integrated with graphene oxide (GO) or conjugated with PSs such as zinc phthalocyanine (ZnPc) or chlorin e6 (Ce6), AuNPs markedly increase ROS generation even under low-intensity irradiation. Their geometry (e.g., nanorods, nanostars, nanoshells) can also be tuned to shift SPR into the NIR region, enabling deeper tissue penetration and improving PDT efficacy.[57]

AuNPs additionally possess highly tunable surface chemistry, supporting functionalization with PEG, folic acid, RGD peptides, or monoclonal antibodies to enhance circulation stability and tumor targeting. Many AuNP-based platforms also enable combined PDT/PTT, where NIR-induced photothermal heating synergizes with PS activation to enhance overall therapeutic performance.[58]

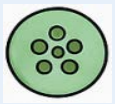
Ferrite Nanoparticles (Fe_3O_4)

Superparamagnetic iron oxide nanoparticles (Fe_3O_4

Table 7. Together, these ligands transform GO into a precision nanoplatform, enabling smart delivery of therapeutics with enhanced targeting efficiency, reduced systemic toxicity, and minimal uptake by healthy tissues.

LIGAND	Target receptor	Target cell/tissue	Advantages	Mechanism	[Ref]
FOLIC ACID 	Folate receptor	Epithelial cancers	High selectivity well-known receptor	Receptor–Mediated Endocytosis	52
RGD PEPTIDE 	Integrin αvβ3	Angiogenic tumor Vasculature, metastatic tumors	Promotes tumor homing and deep penetration	Specific binding to integrins	53
APTAMERS 	Protein or surface antigens	Cancer cells with specific biomarkers	high selectivity, immunogenicity, and versatility	Mechanism: Structure-specific molecular binding	54
ANTIBODIES 	Specific cell surface receptors	Superior specificity immune pathway engagement	Antigen–Antibody interaction	Antigen–Antibody interaction	55

Table 8. Gold nanoparticles utilize surface plasmon resonance for efficient light absorption and multifunctional use in drug delivery and photothermal therapy. Magnetic nanoparticles enable targeted delivery and dual imaging through magnetic guidance and Fenton-based ROS generation. Silver nanoparticles provide strong antimicrobial and ROS-mediated cytotoxic effects but require cautious use due to dose-dependent toxicity.

Metal/Magnetic Nanoparticle	Properties	Application	Considerations	Ref.
Gold Nanoparticles (AuNPs) 	Surface plasmon resonance	PDT, drug delivery, imaging	Versatile functionalization of PTT	57,58
Magnetic Nanoparticles (Fe_3O_4) 	Magnetic responsiveness, Fenton reactions	PDT, Magnetic targeting, dual imaging	MRI contrast biocompatible coating	59,60,61,62
Silver Nanoparticles (AgNPs) 	Antimicrobial cytotoxic	PDT, ROS generation, antibacterial action	Dose-dependent toxicity surface modification	64,65

NPs) are widely applied in biomedical systems due to their magnetic responsiveness, biocompatibility, and strong T_2-weighted MRI contrast. In PDT, they serve as magnetically guided nanocarriers that enable controlled accumulation of therapeutic agents at tumor sites under an external magnetic field.[59]

Fe_3O_4 NPs also possess intrinsic nanozyme activity, catalyzing Fenton and Fenton-like reactions in the acidic tumor microenvironment to convert endogenous H_2O_2 into highly cytotoxic hydroxyl radicals (•OH). This catalytic ROS generation complements photosensitizer-mediated singlet oxygen ($^1O_2$) production, thereby enhancing overall photodynamic efficacy.[60]

GO–Fe_3O_4 hybrids combine magnetic targeting, improved cellular internalization, and dual-modal imaging (MRI and fluorescence), while strengthening PDT performance through catalytic •OH production and controllable photosensitizer release.[61,62] To improve physiological stability, Fe_3O_4 NPs are commonly coated with biocompatible polymers such as PEG or dextran to reduce aggregation, prolong circulation, and minimize opsonization.[6]

Silver Nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) exhibit strong cytotoxic and antimicrobial properties through disruption of mitochondrial function, membrane integrity, and oxidative balance. In PDT, their surface plasmon resonance (SPR) enhances light absorption and electron transfer, increasing ROS generation.[56,63]

When combined with photosensitizers, AgNPs improve photoactivation and ROS yield, including superoxide and hydroxyl radicals, while also inducing mitochondrial dysfunction and DNA damage that sensitize cancer cells to phototoxicity.[64,65] GO–AgNP composites further provide high drug/PS loading, enhanced light-triggered

ROS production, and additional antimicrobial activity beneficial for managing tumor-associated infections.[66]

However, concerns remain regarding dose-dependent cytotoxicity, tissue accumulation, and limited clearance; therefore, strategies such as biopolymer coatings, PEGylation, and green synthesis are being explored to improve safety.[67]

Chemo–PDT/PTT Synergistic Strategies in Cancer Therapy

The combination of chemotherapy with photodynamic (PDT) or photothermal therapy (PTT) represents a multimodal strategy that enhances anticancer efficacy through complementary cytotoxic mechanisms and helps overcome limitations of conventional chemotherapy, including poor tumor selectivity and multidrug resistance.[11,57]

In PDT, photosensitizers generate reactive oxygen species (ROS) upon light activation, whereas PTT converts absorbed NIR light into localized hyperthermia that disrupts cellular structures [68]. When combined with chemotherapy, PDT-generated ROS weaken antioxidant defenses and sensitize tumor cells to drugs, while PTT-induced hyperthermia increases vascular permeability, enhances drug penetration, and suppresses DNA repair, allowing dose reduction and lowering systemic toxicity.[68,69]

Such chemo–PDT/PTT strategies can overcome multidrug resistance by targeting multiple survival pathways simultaneously.[70] Advances in nanotechnology have enabled multifunctional nanoplatforms that co-deliver chemotherapeutics, photosensitizers, and photothermal agents, improving tumor biodistribution, controlled release, and therapeutic outcomes compared with monotherapies.[68,70]

Smart Stimuli-Responsive Systems (pH / NIR / Enzyme-Responsive)

GO-based smart delivery systems have attracted significant attention due to their stimuli-responsive behavior, large surface area, photothermal properties, and high drug loading capacity. These systems can respond to acidic pH, overexpressed enzymes, or near-infrared (NIR) irradiation in the tumor microenvironment, enabling spatiotemporally controlled drug release while minimizing systemic toxicity.[71,72]

pH-Responsive Systems

Tumor tissues exhibit a slightly acidic extracellular pH (6.5–6.8) compared with normal tissues (pH 7.4), mainly due to hypoxia-induced glycolysis (Warburg effect), which can be exploited for tumor-selective drug release.

For instance, chitosan-functionalized rGO hydrogels show enhanced doxorubicin release under acidic conditions, improving chemo-photothermal therapy outcomes.[73] Similarly, rGO nanosponges incorporating gold nanorods enable dual pH- and NIR-responsive drug release, enhancing localized treatment efficacy in lung cancer models.[72]

NIR-Responsive Systems

GO exhibits high NIR photothermal conversion efficiency (700–1100 nm), enabling light-controlled drug release via localized heating. In thermoresponsive systems, NIR irradiation induces structural changes that accelerate drug diffusion.

For example, chitosan-functionalized rGO nanogels rapidly release doxorubicin (~42 °C) under 808 nm irradiation, enabling controlled chemo-photothermal therapy.[73] Similarly, amino-terminated hyperbranched polymer-modified rGO systems show synergistic chemo-photothermal effects, with accelerated drug release under combined NIR irradiation and acidic conditions.[74]

Enzyme-Responsive Systems

Overexpressed proteases in the tumor microenvironment provide an endogenous trigger for selective drug release. Gated mesoporous carriers functionalized with enzyme-cleavable polymers (e.g., poly-L-glutamic acid, PGA) act as molecular valves that degrade in response to protease activity, releasing payloads specifically at tumor sites while limiting off-target effects (Table 9).[75]

Multi-Stimuli Responsive Platforms

Multi-functional GO-based systems integrating multiple stimuli (pH, NIR, enzymes) have been designed to further improve precision and therapeutic efficacy. For example, supramolecular cyclodextrin-functionalized GO hydrogels respond concurrently to pH, NIR irradiation, and temperature, enabling finely tuned spatiotemporal control of drug release.[61,72] Such platforms enhance tumor specificity and therapeutic potency while reducing systemic toxicity.

Graphene Oxide Hybrid Structures with Quantum Dots, Liposomes, and DNA Nanostructures

Graphene oxide (GO), owing to its large specific surface area, abundant oxygen-containing functional groups, tunable photothermal properties, and favorable biocompatibility, has emerged as a highly versatile platform for multimodal biomedical applications. The integration of GO with quantum dots (QDs), liposomes, and DNA nanostructures has enabled the development of multifunctional and stimuli-responsive nanoplatforms with enhanced targeting capability for drug delivery, bioimaging, and cancer theranostics. Such hybrid systems exploit the complementary physicochemical and biological characteristics of their individual components to improve therapeutic efficacy, targeting precision, and controlled drug release behavior.[61,72]

Graphene Oxide–Quantum Dot Hybrids

Quantum dots (QDs) are semiconductor nanocrystals characterized by size-dependent photoluminescence, high quantum yield, and excellent photostability, making them suitable for imaging-guided therapy. Integration with GO enhances colloidal stability, aqueous dispersibility, and biocompatibility under physiological conditions.

Table 9. GO smart delivery systems use tumor stimuli (acidic pH, NIR, enzymes) for controlled drug release. Multi-responsive platforms enhance specificity and reduce systemic toxicity in cancer nanomedicine.

Stimulus Type	Comments	Ref.
pH-Responsive	• Exploits acidic tumor microenvironment (pH ~6.5–6.8) for drug release. • Chitosan-functionalized rGO hydrogels with PEG and carboxymethyl chitosan. • Enhanced chemo-photothermal therapy, site-specific release.	71,72
pH + NIR Dual Responsive	• Combines low pH and NIR-induced heating for controlled release. • rGO hybrid nanosponges with gold nanorods. • Localized treatment and increased efficacy in lung cancer.	73,74
NIR-Responsive	• Mechanism: GO converts NIR light to heat to trigger drug release. • Example System / Material: Chitosan-modified rGO nanogels (808 nm laser). • Feedback-controlled drug delivery at ~42°C.	73
NIR + pH Dual Responsive	• Uses both acidity and heat for synergistic release. • Hyperbranched polymer-modified rGO. • Enhanced combination therapy, higher doxorubicin release.	74
Enzyme-Responsive	• Triggered by tumor-overexpressed proteases (e.g., MMPs). • GO-based gated mesoporous carriers with PGA polymer valves. • Selective tumor release, minimal off-target toxicity.	75
Multi-Stimuli Responsive	• Combines pH, NIR, and enzymatic triggers for precision delivery. • Cyclodextrin-functionalized GO hydrogels. • Finely tuned spatiotemporal drug release, reduced side effects.	61,72

GO–QD hybrids enable multimodal theranostics by combining GO's strong NIR-induced photothermal conversion with the high-resolution fluorescence imaging of QDs, allowing real-time biodistribution tracking alongside photothermal or photodynamic tumor ablation. These constructs demonstrate improved imaging contrast, efficient cellular uptake, and synergistic PTT/PDT effects.

Recent studies further highlight their interactions with biological systems—including modulation of autophagy, immune responses, and redox balance—providing important insights into safety and therapeutic optimization.[76,77]

Graphene Oxide–Liposome Hybrids

Liposomes are biocompatible phospholipid vesicles capable of encapsulating hydrophilic drugs in their aqueous core and hydrophobic agents within the lipid bilayer. Incorporating GO generates hybrid nanostructures that combine GO's photothermal and mechanical properties with the high loading capacity and biocompatibility of liposomes.

GO may be adsorbed onto the outer membrane to enhance structural stability and reduce premature leakage, or embedded within the bilayer to increase rigidity and improve release control. These GO–liposome hybrids enable pH- and NIR-responsive, on-demand drug release, enhancing site-specific chemotherapy while minimizing systemic toxicity.[77,78]

Surface functionalization with targeting ligands (e.g., folic acid, peptides, antibodies) further enables active tumor targeting and improved cellular uptake, resulting in enhanced pharmacokinetics and controlled delivery in combined chemo-PDT/PTT strategies.

Graphene Oxide–DNA Nanostructure Hybrids

DNA nanotechnology offers a programmable platform for designing precise, biocompatible, and stimulus-responsive nanostructures. GO strongly binds single-stranded DNA through π–π stacking and hydrogen bonding, enabling the formation of stable GO–DNA hybrids used in targeted delivery, biosensing, and imaging. DNA aptamers attached to GO function as high-affinity recognition elements for cancer biomarkers, supporting selective drug delivery, enhanced tumor retention, and minimized off-target effects. DNA nanostructures can also undergo stimulus-induced conformational changes triggered by acidic pH, nuclease overexpression, or ionic-strength variations, allowing controlled cargo release from the GO–DNA complex.

Coupled with GO's photothermal activity, these hybrids form multifunctional theranostic platforms capable of simultaneous imaging, drug release, and photothermal tumor ablation (Table 10).[76,79]

Challenges and Future Perspectives

Although GO-based nanocomposites have demonstrated [remarkable potential as photoactive platforms for cancer PDT], several critical barriers must be addressed before they can be translated into clinical applications.

Long-Term Toxicity and Biodistribution

The biodegradation, long-term biocompatibility, organ accumulation, and clearance of GO-based nanomaterials remain insufficiently defined. Their persistence in the RES, particularly the liver and spleen, raises concerns about chronic inflammation and oxidative or fibrotic responses. Surface engineering strategies (PEGylation, zwitterionic coatings, biomembrane cloaking) improve circulation, but their effects on immune recognition and long-term clearance are still unclear. More comprehensive in vivo studies are required to determine dose-dependent toxicity, degradation kinetics, and the long-term fate of GO fragments.[80,81]

Table 10. This table summarizes three distinct graphene oxide-based hybrid structures, comprising quantum dots, liposomes, and DNA nanostructures, and highlights their key features in targeted drug delivery, bioimaging, and stimuli-responsive behavior.

Hybrid System	Features/Comments	[Ref]
GO–Quantum Dots	• Main Components: Graphene Oxide + Semiconductor Quantum Dots. • Key Properties: Strong photoluminescence, Photostability. • Synergistic Benefits: Enhanced imaging + drug delivery (theranostics), Better dispersibility of QDs. • Drug Loading Mechanism: π-π stacking + hydrogen bonding. • Stimuli Responsiveness: pH-sensitive + NIR-triggered (photothermal). • Therapeutic Applications: Fluorescence imaging + photothermal therapy + DOX delivery. • Release Control: NIR light triggers drug release via heat. • Imaging Capability: Excellent (via quantum dot fluorescence). • Targeting Potential: Moderate (can be functionalized).	77,78
GO–Liposomes	• Main Components: Graphene Oxide + Phospholipid Bilayer Vesicles. • Key Properties: High drug encapsulation, Biocompatibility. • Synergistic Benefits: Structural stability prevents premature leakage. • Drug Loading Mechanism: Encapsulation (within liposome) + GO adsorption. • Stimuli Responsiveness: pH-sensitive + NIR-triggered. • Therapeutic Applications: Controlled chemotherapy + photothermal therapy. • Release Control: pH and NIR dual triggers. • Imaging Capability: Moderate (depends on additional agents). • Targeting Potential: High (surface ligands/antibodies possible).	76,77
GO–DNA Nanostructures	• Main Components: Graphene Oxide + DNA (ssDNA, Aptamers, Nanostructures). • Key Properties: Programmability, Biorecognition capabilities. • Synergistic Benefits: Target-specific responsive drug delivery. • Drug Loading Mechanism: π-π stacking on GO + conformational DNA interactions. • Stimuli Responsiveness: pH, enzyme, or thermal responsiveness. • Therapeutic Applications: Biosensing + Targeted delivery + Theranostics. • Release Control: Structural DNA change triggers release. • Imaging Capability: High specificity via aptamer-based recognition. • Targeting Potential: Very High (aptamers provide molecular targeting).	76,79

Challenges and Limitations in Translating Animal Models to Human Responses

Most preclinical evaluations of GO-mediated PDT rely on murine xenograft models, which incompletely reflect human tumor biology. Key differences include tumor vascular architecture, immune modulation, species-dependent pharmacokinetics, and markedly stronger EPR effects observed in mice. In contrast, human tumors display greater microenvironmental heterogeneity, impaired perfusion, and weaker EPR, limiting translational relevance. Advanced models—such as patient-derived organoids, humanized mice, and ex vivo vascularized tumor systems—are therefore essential to bridge the preclinical–clinical gap.[82]

Multi-Functional Smart System Design

Multifunctional GO hybrids integrating stimuli-responsiveness, PDT, PTT, imaging, and chemotherapy show strong potential for precision oncology, but their growing structural complexity creates notable challenges. These include difficulties in reproducible synthesis, batch-to-batch variability, limited scalability, and regulatory barriers associated with multi-component nanoplatforms. Clinical translation will require robust and standardized fabrication protocols, physicochemical stability under physiological conditions, and consistent activation profiles under clinically relevant irradiation parameters.[15]

Lack of Clinical Trials and Regulatory Frameworks

Despite significant preclinical progress, no GO-based PDT nanotherapeutics have advanced into late-stage clinical trials. Key obstacles include limited PK/PD characterization, variability in GO physicochemical properties (size, oxidation state, defect density), the absence of regulatory guidelines specific to two-dimensional nanomaterials, and a lack of GMP-compatible large-scale manufacturing. Progress will require interdisciplinary collaboration across materials science, pharmacology, oncology, toxicology, and regulatory science to establish harmonized standards for characterization, safety assessment, and long-term evaluation. Such frameworks are essential for translating GO-based PDT platforms from bench to bedside.[83,84]

Conclusion

Graphene oxide, with its tunable surface chemistry, high drug-loading capacity, and intrinsic photothermal and photodynamic activity, has become a promising platform for cancer-targeted PDT. This review highlighted advanced GO functionalization strategies, including conjugation with photosensitizers, biocompatible polymers, targeting ligands, and hybrid nanomaterials, which collectively enhance dispersibility, photostability, tumor selectivity, controlled drug release, and ROS generation.

GO-based nanoformulations help overcome the limitations of conventional photosensitizers, such as hydrophobicity, poor bioavailability, and limited tumor accumulation. Moreover, integrating GO-mediated PDT with chemotherapy or PTT yields synergistic antitumor effects with reduced systemic toxicity.

Looking ahead, multifunctional GO-based smart nanoplatforms may significantly advance precision cancer therapy. However, successful clinical translation will require addressing long-term toxicity, interspecies translational gaps, and regulatory challenges.

With continued interdisciplinary collaboration, GO holds strong potential to evolve into a next-generation phototherapeutic and theranostic agent for personalized oncology.

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Competing Interests

There is no conflict of interest.

Ethical Approval

As this study is based exclusively on previously published data and does not involve human participants or animal experiments, ethical approval and informed consent were not required.

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