Functionalized Graphene Quantum Dots for Targeted Drug Delivery and Cancer Theranostics: Advances, Challenges, and Future Perspectives.

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1. Abstract:

Background-

Cancer remains a leading cause of death worldwide, and conventional treatment strategies such as chemotherapy and radiotherapy are often limited by poor selectivity, systemic toxicity, and drug resistance. These limitations necessitate the development of advanced drug delivery systems. Nanotechnology has emerged as a promising approach, with graphene quantum dots (GQDs) gaining significant attention due to their unique physicochemical and optical properties.

Objective-

This review aims to critically evaluate the role of functionalized graphene quantum dots in enhancing drug delivery efficiency and improving therapeutic outcomes in cancer treatment.

Main Content-

The review discusses various synthesis methods of GQDs, including top-down and bottom-up approaches, along with their advantages and limitations. It further highlights different functionalization strategies, such as covalent and non-covalent modifications, which enhance stability, targeting capability, and drug loading efficiency. Additionally, the mechanisms of drug loading and controlled release are explored, with emphasis on stimuli-responsive systems. The application of functionalized GQDs in cancer therapy, including targeted chemotherapy, photothermal therapy, and photodynamic therapy, is examined in detail, along with their underlying anticancer mechanisms.

Conclusion-

Functionalized graphene quantum dots offer a versatile and efficient platform for targeted drug delivery and cancer therapy. Despite promising results, challenges related to scalability, toxicity, and clinical translation remain. Future research is expected to advance their role in personalized nanomedicine.

2. Keywords:

Graphene quantum dots (GQDs); Functionalized nanomaterial's ; Targeted drug delivery; Cancer therapy; Nano carriers; Controlled drug release; Photo thermal therapy (PTT); Photodynamic therapy (PDT); Theranostics; Nanomedicine

How to cite this article: Pawar SV, Jain BV. Functionalized graphene quantum dots for targeted drug delivery and cancer theranostics: advances, challenges, and future perspectives. Int J Drug Deliv Technol. 2026;16(73s): 141-158. DOI: 10.25258/ijddt.16.73s.16

3. Introduction:

3.1. Global Burden of Cancer-

Cancer remains a major global health concern and is one of the leading causes of morbidity and mortality worldwide. According to recent global health estimates, cancer accounts for approximately one in six deaths, with a continuously increasing number of new cases reported annually [1]. This rising incidence is largely attributed to population aging, environmental exposure, sedentary lifestyles, and genetic susceptibility. Among various cancer types, lung, breast, colorectal, and prostate cancers are the most prevalent, contributing significantly to global cancer-related deaths.

Despite notable advancements in early detection techniques and therapeutic interventions, the overall

survival rate for many cancers remains suboptimal. Late-stage diagnosis and limited treatment efficacy continue to be major challenges in clinical oncology. Therefore, the growing global burden of cancer necessitates the development of more efficient, targeted, and safer therapeutic strategies aimed at improving patient outcomes while minimizing adverse effects [2].

3.2. Limitations of Conventional Cancer Therapy-

Conventional cancer treatment modalities, including chemotherapy, radiotherapy, and surgical interventions, have long been established as standard approaches in oncology. However, these therapies are associated with several inherent limitations that significantly compromise their effectiveness. One of the most critical drawbacks is chemotherapy-induced toxicity, wherein anticancer agents fail to distinguish between malignant and healthy rapidly dividing cells. This non-selective action leads to severe side effects such as immunosuppression, gastrointestinal disturbances, alopecia, and organ toxicity [3]. In addition, the lack of specificity results in non-targeted drug distribution, thereby reducing therapeutic efficiency and increasing systemic exposure.

Another major challenge is the emergence of multidrug resistance (MDR), a phenomenon in which cancer cells develop resistance to multiple chemotherapeutic agents. This resistance is mediated through mechanisms such as increased drug efflux, genetic mutations, and alterations in cellular signaling pathways, ultimately leading to treatment failure [4]. Furthermore, many anticancer drugs exhibit poor bioavailability, limiting their effective concentration at the target site. Collectively, these limitations highlight the urgent need for advanced drug delivery systems capable of overcoming these barriers. These challenges have driven the exploration of innovative approaches, particularly those based on nanotechnology [5].

3.3. Role of Nanotechnology in Cancer Treatment-

Nanotechnology has emerged as a revolutionary platform in cancer therapy, offering innovative solutions for improving drug delivery and therapeutic efficacy. Nanoscale drug delivery systems, commonly referred to as nanocarriers, include liposomes, polymeric nanoparticles, dendrimers, and carbon-based nanomaterials, each designed to enhance the pharmacokinetic and pharmacodynamic profiles of anticancer drugs [6].

A key advantage of nanotechnology lies in its ability to exploit the enhanced permeability and retention (EPR) effect, which enables nanoparticles to preferentially accumulate within tumor tissues due to their leaky vasculature. This selective accumulation leads to increased drug concentration at the tumor site while reducing systemic toxicity [7]. Moreover, nanotechnology enables the development of targeted drug delivery systems, where nanocarriers are functionalized with ligands such as antibodies, peptides, or small molecules that specifically recognize cancer cell receptors. This targeted approach significantly enhances therapeutic precision and minimizes damage to healthy tissues. Consequently, nanotechnology has substantially advanced the development of safer, more efficient, and patient-specific cancer treatment strategies [8].

3.4. Introduction to Graphene Quantum Dots (GQDs)-

Graphene quantum dots (GQDs) represent a novel class of zero-dimensional carbon-based nanomaterials derived from graphene. Typically measuring less than 10 nm in size, GQDs exhibit unique physicochemical properties arising from quantum confinement and edge effects [9]. Structurally, they consist of sp^2-hybridized carbon atoms arranged in a hexagonal lattice, similar to graphene, but confined to nanoscale dimensions.

One of the most distinctive features of GQDs is their intrinsic photoluminescence, which makes them highly suitable for bioimaging and diagnostic applications. Additionally, GQDs possess excellent water solubility, chemical stability, and biocompatibility, rendering them highly attractive for biomedical applications, particularly in drug delivery and cancer therapy [10]. Compared to other nanomaterials, GQDs offer several advantages, including low toxicity, ease of synthesis, and versatile surface modification capabilities. These properties position GQDs as promising candidates in the field of nanomedicine.

3.5. Importance of Functionalization-

Although graphene quantum dots exhibit several intrinsic advantages, their performance in biological environments can be significantly enhanced through functionalization. Functionalization involves the modification of the GQD surface with various chemical groups, polymers, or targeting ligands to improve their physicochemical stability and biological interactions. One of the primary benefits of functionalization is the enhancement of targeting capability, enabling GQDs to selectively accumulate in tumor tissues. This is typically achieved through the conjugation of targeting ligands such as folic acid, antibodies, or peptides that recognize overexpressed receptors on cancer cells [11].

In addition, functionalization improves drug loading capacity by introducing active binding sites that facilitate the attachment or encapsulation of therapeutic agents. It also enhances the stability and circulation time of GQDs in physiological conditions by preventing aggregation and premature clearance.

These modifications are crucial for optimizing GQDs as efficient nanocarriers in drug delivery systems [12].

3.6. Aim and Scope of the Review-

The present review aims to provide a comprehensive and critical evaluation of functionalized graphene quantum dots in the context of drug delivery and cancer therapy. It systematically examines various synthesis methods, surface functionalization strategies, and mechanisms involved in drug loading and controlled release. Furthermore, the review explores the application of functionalized GQDs in advanced cancer treatment modalities, including targeted chemotherapy, photothermal therapy, and photodynamic therapy. Emphasis is placed on their therapeutic efficiency, biocompatibility, and potential for clinical translation.

In addition, this review highlights current challenges, including large-scale production, toxicity concerns, and regulatory limitations, while also discussing future perspectives. Particular attention is given to emerging trends such as multifunctional nanocarriers and personalized nanomedicine. Overall, this work aims to bridge the gap between experimental research and clinical application of GQDs in oncology.

4. Graphene Quantum Dots: Structure and Properties:

4.1. Structure of Graphene Quantum Dots-

Graphene quantum dots (GQDs) are nanoscale fragments of graphene that exhibit unique structural characteristics due to their reduced dimensionality and quantum confinement effects. At the atomic level, GQDs are composed of a carbon lattice structure in which carbon atoms are arranged in a two-dimensional hexagonal honeycomb pattern. This arrangement is similar to that of bulk graphene; however, in GQDs, the lateral dimensions are confined to the nanoscale, typically below 10 nm, resulting in distinct electronic and optical properties [13].

A fundamental feature of GQDs is the presence of sp^2 hybridization of carbon atoms. In this configuration, each carbon atom forms three sigma (σ) bonds with neighboring carbon atoms, creating a planar structure, while the remaining unhybridized p-orbital contributes to a delocalized π-electron system. This extended π-conjugation plays a crucial role in determining the electronic behavior and optical activity of GQDs, including their fluorescence properties [14].

The nanoscale size of GQDs is a defining characteristic that leads to quantum confinement and edge effects. As the size of the graphene sheet decreases to the nanometer range, discrete energy levels are formed, resulting in size-dependent optical and electronic properties. Additionally, the presence of edge defects and functional groups further influences their reactivity and interaction with biological systems. These structural attributes collectively contribute to the versatility of GQDs in biomedical applications. The structural features and surface functional groups of GQDs are illustrated in Figure 1.

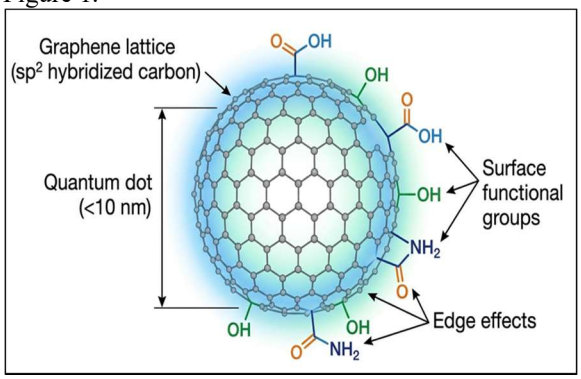

Figure 1. Structure and surface functionalization of graphene quantum dots (GQDs), showing nanoscale size, hexagonal carbon lattice, and surface functional groups.

4.2. Physicochemical Properties-

Graphene quantum dots exhibit a range of unique physicochemical properties that make them highly suitable for drug delivery and cancer therapy applications. One of the most important properties is photoluminescence, which arises due to quantum confinement and surface states. GQDs can emit fluorescence across a broad spectrum, depending on their size, shape, and surface chemistry. This property is particularly advantageous for bioimaging and diagnostic applications, as it allows real-time tracking of nanoparticles within biological systems [15]. Another key feature is their high surface area, which provides abundant active sites for drug loading and surface modification. The large surface-to-volume ratio enhances the interaction between GQDs and therapeutic molecules, thereby improving drug loading efficiency and delivery performance [16].

GQDs also exhibit excellent water solubility, primarily due to the presence of oxygen-containing functional groups such as hydroxyl, carboxyl, and epoxy groups on their surface. This property facilitates their dispersion in aqueous biological environments and enhances their compatibility with physiological systems [17]. In terms of biological interaction, GQDs demonstrate remarkable biocompatibility, making them safer alternatives to many metal-based nanoparticles. Their low cytotoxicity and minimal immunogenic response are critical factors for their application in drug delivery and biomedical imaging [18].

Furthermore, GQDs possess significant chemical stability, which ensures their structural integrity under physiological conditions. This stability is essential for maintaining consistent performance during circulation

and therapeutic action, especially in complex biological environments [19].

4.3. Advantages in Biomedical Applications-

The unique structural and physicochemical properties of graphene quantum dots provide several advantages that make them highly suitable for biomedical applications, particularly in drug delivery and cancer therapy. One of the primary advantages is their ease of surface modification. The presence of functional groups on the surface of GQDs allows for straightforward conjugation with drugs, polymers, and targeting ligands. This flexibility enables the design of multifunctional nanocarriers tailored for specific therapeutic applications [20].

Another significant benefit is their low toxicity, which distinguishes GQDs from many other nanomaterials, particularly heavy metal-based quantum dots. Their favorable safety profile enhances their potential for clinical applications, reducing the risk of adverse side effects [21]. Additionally, GQDs exhibit excellent imaging capability due to their intrinsic photoluminescent properties. This allows them to function as both therapeutic and diagnostic agents, enabling simultaneous drug delivery and real-time monitoring of treatment, a concept commonly referred to as theranostics [22].

Overall, the combination of easy functionalization, biocompatibility, and imaging potential positions graphene quantum dots as highly promising nanomaterials in modern biomedical research and nanomedicine.

5. Synthesis Methods of Graphene Quantum Dots:

The synthesis of graphene quantum dots (GQDs) plays a crucial role in determining their size, surface properties, and overall performance in biomedical applications. Broadly, GQD synthesis methods are classified into top-down and bottom-up approaches, each with distinct principles, advantages, and limitations. The choice of method significantly influences particle size distribution, yield, scalability, and functionalization potential.

5.1. Top-Down Approaches-

Top-down approaches involve the breakdown of larger carbon structures such as graphite, graphene sheets, or carbon fibers into nanoscale graphene quantum dots. These methods are widely used due to their simplicity and scalability.

- **Chemical Oxidation**

Principle:

Chemical oxidation involves the use of strong oxidizing agents (e.g., nitric acid, sulfuric acid, or potassium permanganate) to cleave bulk carbon materials into smaller graphene fragments. The oxidation process introduces oxygen-containing functional groups, which facilitate the formation of GQDs [23].

Advantages:

1. Simple and cost-effective method
2. Suitable for large-scale production
3. Produces water-soluble GQDs due to surface functional groups

Disadvantages:

1. Poor control over particle size and uniformity
2. Use of harsh chemicals may introduce defects
3. Requires extensive purification steps

- **Electrochemical Exfoliation**

Principle:

In this method, an electrical potential is applied to graphite electrodes immersed in an electrolyte solution. The applied voltage induces oxidation and exfoliation of graphite layers, leading to the formation of GQDs [24].

Advantages:

1. Environmentally friendly compared to chemical methods
2. Better control over reaction conditions
3. Relatively high purity of final product

Disadvantages:

1. Requires specialized equipment
2. Limited scalability compared to chemical oxidation
3. Particle size distribution may still vary

- **Laser Ablation**

Principle:

Laser ablation involves irradiating a carbon source (such as graphite) with high-energy laser pulses, resulting in the fragmentation of the material into nanoscale GQDs. The process is typically carried out in a controlled atmosphere or liquid medium [25].

Advantages:

1. Produces high-purity GQDs
2. No need for chemical reagents
3. Minimal contamination

Disadvantages:

1. Expensive instrumentation
2. Low yield
3. Difficult to scale up for industrial applications

5.2. Bottom-Up Approaches-

Bottom-up approaches involve the synthesis of GQDs from small organic molecules or carbon precursors through controlled chemical reactions. These methods offer better control over particle size and structural properties.

- **Hydrothermal Synthesis**

Principle:

Hydrothermal synthesis involves heating organic precursors (such as citric acid or glucose) in a sealed

autoclave under high temperature and pressure. This leads to carbonization and nucleation, forming GQDs [26].

Advantages:

1. Good control over particle size and morphology
2. Simple and reproducible method
3. High-quality GQDs with uniform properties

Disadvantages:

1. Time-consuming process
2. Requires high-pressure equipment
3. Moderate scalability

- **Microwave Synthesis**

Principle:

Microwave-assisted synthesis uses microwave radiation to rapidly heat carbon precursors, leading to quick carbonization and formation of GQDs. The process significantly reduces reaction time [27].

Advantages:

1. Rapid synthesis (minutes instead of hours)
2. Energy-efficient
3. Uniform heating leads to consistent particle formation

Disadvantages:

1. Limited control over large-scale production
2. Requires microwave reactor setup
3. Potential for uneven particle distribution in some cases

- **Carbonization Methods**

Principle:

Carbonization involves the thermal decomposition of organic materials (e.g., biomass, polymers) at elevated temperatures to produce carbon-based nanostructures, including GQDs [28].

Advantages:

1. Utilizes low-cost and renewable precursors
2. Environmentally friendly approach
3. Suitable for large-scale production

Disadvantages:

1. Less control over particle size
2. Possibility of impurities
3. Requires post-synthesis purification

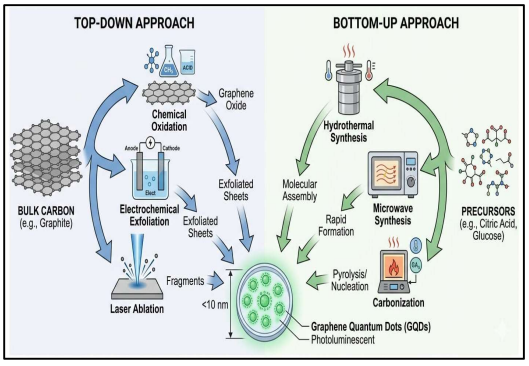

Figure 2. Schematic illustration of top-down and bottom-up synthesis approaches for graphene quantum dots, highlighting fragmentation of bulk carbon materials and assembly from molecular precursors.

5.3. Comparison of Synthesis Methods:

The selection of an appropriate synthesis method depends on several factors, including particle size control, yield, scalability, and intended application. Top-down approaches are generally preferred for large-scale production due to their simplicity, whereas bottom-up approaches offer better control over particle size and structural uniformity.

In terms of particle size control, bottom-up methods such as hydrothermal and microwave synthesis provide more precise control compared to top-down techniques. Regarding yield, chemical oxidation and carbonization methods are more favorable for bulk production. However, scalability remains a challenge for methods like laser ablation and microwave synthesis due to equipment limitations. A comparative summary of different synthesis methods is presented in Table 1.

Table 1: Comparison of Graphene Quantum Dot Synthesis Methods

Method	Approach	Principle	Advantages	Limitations
Chemical Oxidation	Top-down	Oxidative cutting of carbon materials	Simple, scalable	Poor size control, harsh chemicals
Electrochemical Exfoliation	Top-down	Electrical exfoliation of graphite	Eco-friendly, high purity	Limited scalability
Laser Ablation	Top-down	Laser-induced fragmentation	High purity	Expensive, low yield
Hydrothermal	Bottom-up	High temp-pressure carbonization	Good size control	Time-consuming
Microwave	Bottom-up	Rapid microwave heating	Fast, energy-efficient	Scale-up challenges
Carbonization	Bottom-up	Thermal decomposition of	Low-cost, eco-	Less uniform

		precursors	friendly	particles

6. Functionalization of Graphene Quantum Dots:

Functionalization is a critical strategy employed to enhance the performance of graphene quantum dots (GQDs) in biomedical applications. Although GQDs inherently possess favorable properties such as small size, photoluminescence, and biocompatibility, their interaction with biological systems can be significantly improved through surface modification. Functionalization involves the introduction of chemical groups, polymers, or biological ligands onto the surface of GQDs, thereby tailoring their physicochemical and biological characteristics for specific applications, particularly in targeted drug delivery and cancer therapy.

6.1. Need for Functionalization-

The necessity for functionalization arises from the requirement to optimize GQDs for efficient performance in complex biological environments. One of the primary advantages is improved targeting capability, where functionalized GQDs can selectively accumulate in tumor tissues. This is achieved by attaching specific ligands that recognize receptors overexpressed on cancer cells, thereby enhancing site-specific drug delivery and minimizing off-target effects [29].

Functionalization also contributes to enhanced stability by preventing aggregation of nanoparticles under physiological conditions. Surface modification improves dispersion in aqueous media and prolongs circulation time in the bloodstream, which is essential for effective drug delivery [30]. In addition, functionalization significantly increases drug loading capacity. The introduction of functional groups provides active binding sites for the attachment or encapsulation of therapeutic agents, resulting in higher drug payloads and improved delivery efficiency. These combined benefits make functionalization an indispensable step in the development of GQD-based nanocarriers.

6.2. Covalent Functionalization-

Covalent functionalization involves the formation of strong chemical bonds between functional groups and the surface of GQDs. This approach provides enhanced stability and long-term retention of functional moieties, making it highly suitable for biomedical applications.

- **PEGylation**

PEGylation refers to the attachment of polyethylene glycol (PEG) chains to the surface of GQDs. This modification improves water solubility, reduces protein adsorption, and minimizes recognition by the immune system. As a result, PEGylated GQDs exhibit prolonged circulation time and enhanced bioavailability, which significantly improves drug delivery efficiency [31].

- **Amination**

Amination involves the introduction of amine ($-NH_2$) groups onto the surface of GQDs. These functional groups facilitate the binding of drugs and biomolecules through covalent or electrostatic interactions. Aminated GQDs also enhance cellular uptake due to their positive charge, which promotes interaction with negatively charged cell membranes [32].

- **Carboxylation**

Carboxylation introduces carboxyl (-COOH) groups onto the GQD surface, increasing their hydrophilicity and providing reactive sites for further conjugation with drugs or targeting ligands. This modification enhances drug loading capacity and allows for controlled release of therapeutic agents under specific physiological conditions [33].

Overall, covalent functionalization improves the stability, targeting ability, and drug delivery efficiency of GQDs by enabling strong and stable interactions with therapeutic molecules.

6.3. Non-Covalent Functionalization-

Non-covalent functionalization relies on weak intermolecular interactions to modify the surface of GQDs without altering their core structure. This approach preserves the intrinsic electronic and optical properties of GQDs, making it advantageous for applications requiring fluorescence and imaging.

- **π–π Stacking**

π–π stacking interactions occur between the aromatic rings of GQDs and drug molecules, particularly those with planar structures such as doxorubicin. This interaction enables efficient drug loading without the need for chemical modification, preserving the functional integrity of both the drug and the nanocarrier [34].

- **Hydrogen Bonding**

Hydrogen bonding involves the interaction between hydrogen donors and acceptors present on the surface of GQDs and drug molecules. This mechanism contributes to stable drug loading and can be influenced by environmental conditions such as pH, enabling controlled drug release [35].

- **Electrostatic Interactions**

Electrostatic interactions arise from the attraction between oppositely charged species. Positively or negatively charged GQDs can interact with charged drug molecules or biomolecules, facilitating drug loading and cellular uptake. These interactions are reversible, allowing for stimuli-responsive drug release in biological environments [36].

Non-covalent functionalization offers a flexible and efficient approach for drug delivery, particularly when preservation of GQD properties is essential.

6.4. Targeting Ligands:

The incorporation of targeting ligands onto functionalized GQDs plays a vital role in achieving precise and efficient cancer therapy. These ligands enable selective recognition and binding to specific receptors that are overexpressed on cancer cells, thereby enhancing targeted drug delivery.

- **Folic Acid**

Folic acid is one of the most widely used targeting ligands due to its high affinity for folate receptors, which are commonly overexpressed in various cancer cells. Conjugation of folic acid to GQDs facilitates receptor-mediated endocytosis, leading to enhanced cellular uptake and improved therapeutic efficacy [37].

- **Antibodies**

Antibodies provide high specificity toward target antigens expressed on cancer cells. Functionalization of GQDs with monoclonal antibodies allows for highly selective targeting, reducing off-target effects and increasing the precision of drug delivery [38].

- **Peptides**

Peptides, such as RGD (arginine-glycine-aspartic acid), are commonly used as targeting ligands due to their ability to bind to integrin receptors on tumor cells. Peptide-functionalized GQDs exhibit enhanced tumor targeting and improved penetration into cancer tissues [39].

The use of targeting ligands significantly improves the therapeutic performance of GQDs by enabling selective accumulation at tumor sites, reducing systemic toxicity, and enhancing treatment outcomes in cancer therapy**.**

The various functionalization strategies employed for graphene quantum dots are schematically illustrated in Figure 3.

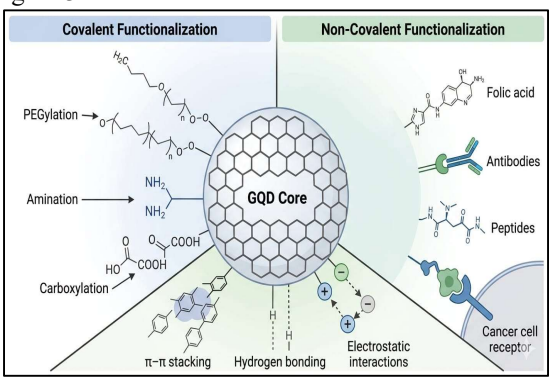

Figure 3: Schematic illustration of functionalization strategies of graphene quantum dots, including covalent and non-covalent modifications and the incorporation of targeting ligands for enhanced drug delivery and cancer therapy.

Table 2: Effect of Functionalization on Drug Delivery Performance

Functionalization Type	Example Ligand	Drug Used	Targeting Mechanism	Key Outcome
PEGylation	PEG	Doxorubicin	Passive (EPR effect)	Increased circulation time
Folic Acid	FA	Paclitaxel	Folate receptor targeting	Enhanced tumor uptake
Antibody Conjugation	Anti-HER2	Doxorubicin	Active targeting	High specificity
Peptide Functionalization	RGD peptide	Cisplatin	Integrin targeting	Improved cellular uptake
pH-sensitive groups	Hydrazone bond	DOX	Tumor pH-triggered release	Controlled drug release

7. Functionalized GQDs as Drug Delivery Systems:

Functionalized graphene quantum dots (GQDs) have emerged as highly efficient nanocarriers for drug delivery due to their unique structural features, large surface area, and versatile surface chemistry. Their ability to interact with a wide range of therapeutic molecules, combined with controlled release capabilities, makes them particularly suitable for targeted cancer therapy. The incorporation of functional groups and targeting ligands further enhances their performance by improving drug loading efficiency, stability, and site-specific delivery.

7.1. Drug Loading Mechanisms-

The effectiveness of GQDs as drug delivery systems largely depends on their ability to efficiently load therapeutic agents. Drug loading onto GQDs is primarily governed by various intermolecular interactions, which allow stable attachment of drugs without compromising their activity.

One of the most prominent mechanisms is π–π stacking, which occurs between the aromatic structure

of GQDs and planar drug molecules such as doxorubicin. This interaction enables strong yet reversible binding, allowing efficient drug loading while preserving the structural integrity of both the drug and the carrier [40]. Another important mechanism is hydrogen bonding, where hydrogen donors and acceptors present on both GQDs and drug molecules interact to form stable complexes. This type of interaction contributes to enhanced drug retention and can be influenced by environmental conditions such as pH, thereby facilitating controlled drug release [41].

In addition, electrostatic interactions play a significant role in drug loading. These interactions arise from the attraction between oppositely charged functional groups present on GQDs and drug molecules. For instance, positively charged drugs can bind to negatively charged GQD surfaces, improving loading efficiency and enabling controlled release under specific physiological conditions [42].

7.2. Controlled Drug Release-

A key advantage of functionalized GQDs is their ability to achieve controlled and stimuli-responsive drug release, which ensures that therapeutic agents are released specifically at the target site, thereby enhancing treatment efficacy and minimizing side effects.

One of the most widely studied mechanisms is pH-responsive drug release. Tumor microenvironments are typically more acidic than normal tissues. Functionalized GQDs can be designed to release drugs in response to this acidic environment, ensuring selective drug delivery to cancer cells while sparing healthy tissues [43]. Another important mechanism is redox-responsive drug release, which exploits the higher concentration of reducing agents such as glutathione in cancer cells. GQDs functionalized with redox-sensitive linkages can release drugs upon exposure to these intracellular conditions, enabling precise and efficient drug delivery [44].

Additionally, enzyme-responsive systems utilize enzymes that are overexpressed in tumor tissues to trigger drug release. In such systems, specific enzymatic reactions cleave the bonds between GQDs and drug molecules, resulting in localized drug release at the tumor site [45].

These stimuli-responsive mechanisms significantly improve the specificity and effectiveness of GQD-based drug delivery systems.

7.3. Advantages of GQD Drug Delivery-

Functionalized GQDs offer several advantages over conventional drug delivery systems, making them highly promising for cancer therapy. One of the most significant advantages is targeted drug delivery, which is achieved through surface functionalization with ligands that specifically recognize cancer cell receptors. This targeted approach enhances drug accumulation at the tumor site and reduces off-target effects [46]. Another key benefit is reduced toxicity, as GQDs enable localized drug release, minimizing exposure of healthy tissues to cytotoxic agents. Their inherent biocompatibility further contributes to their safety profile, making them suitable for clinical applications [47].

Furthermore, GQDs improve bioavailability of therapeutic agents by enhancing solubility, stability, and circulation time in the bloodstream. This ensures that a higher concentration of the drug reaches the target site, thereby improving therapeutic outcomes [48]. Overall, the combination of efficient drug loading, controlled release, and targeted delivery makes functionalized GQDs a powerful platform for advanced drug delivery systems.

The mechanism of drug loading, targeted delivery, and controlled release using functionalized GQDs is schematically illustrated in Figure 4.

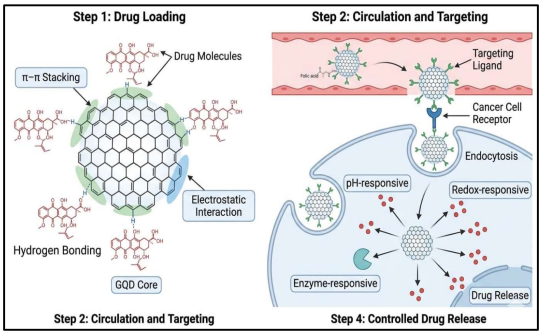

Figure 4: Schematic representation of drug loading, targeted delivery, and stimuli-responsive release of therapeutic agents using functionalized graphene quantum dots in cancer therapy.

8. Applications in Cancer Therapy:

Functionalized graphene quantum dots (GQDs) have demonstrated remarkable potential in cancer therapy due to their multifunctional properties, including efficient drug loading, targeted delivery, photothermal conversion, and photodynamic activity. Their nanoscale size and modifiable surface enable precise interaction with tumor cells, thereby enhancing therapeutic efficacy while minimizing adverse effects. This section highlights the major applications of GQDs in cancer treatment.

8.1. Targeted Chemotherapy-

Targeted chemotherapy using functionalized GQDs has emerged as an effective strategy to improve the therapeutic index of anticancer drugs. By conjugating chemotherapeutic agents with GQDs, it is possible to achieve selective delivery to tumor tissues, thereby reducing systemic toxicity and enhancing drug efficacy. One widely studied example is doxorubicin-

loaded GQDs. Doxorubicin (DOX), an anthracycline anticancer drug, can be efficiently loaded onto GQDs through π–π stacking and electrostatic interactions. Upon administration, the functionalized GQDs accumulate at tumor sites via the enhanced permeability and retention (EPR) effect and ligand-mediated targeting. Once internalized by cancer cells through endocytosis, the acidic intracellular environment triggers the release of DOX, which intercalates with DNA and inhibits topoisomerase II, leading to apoptosis of cancer cells [49].

Similarly, paclitaxel delivery using GQDs has shown promising results. Paclitaxel, a hydrophobic anticancer drug, can be loaded onto functionalized GQDs to improve its solubility and bioavailability. The GQD-based delivery system enhances cellular uptake and facilitates controlled drug release within tumor cells, where paclitaxel stabilizes microtubules and inhibits cell division, ultimately inducing cell death [50].

Thus, GQD-mediated targeted chemotherapy significantly improves drug accumulation at tumor sites while minimizing damage to healthy tissues.

8.2. Photothermal Therapy (PTT)-

Photothermal therapy (PTT) is an emerging non-invasive treatment modality in which nanomaterials convert absorbed light energy into heat, leading to localized tumor destruction. Functionalized GQDs exhibit excellent photothermal conversion efficiency, making them suitable candidates for PTT. Upon irradiation with near-infrared (NIR) light, GQDs absorb the energy and convert it into heat. This localized heat generation increases the temperature of tumor tissues, typically above 42–45°C, which results in thermal ablation of cancer cells [51].

The elevated temperature disrupts cellular structures, denatures proteins, and damages tumor vasculature, ultimately leading to tumor cell death. Additionally, the use of GQDs enables selective targeting of tumor tissues, thereby minimizing damage to surrounding healthy cells. The combination of GQDs with targeting ligands further enhances the specificity and effectiveness of photothermal therapy.

8.3. Photodynamic Therapy (PDT)-

Photodynamic therapy (PDT) is another promising approach in cancer treatment that involves the generation of reactive oxygen species (ROS) to induce cancer cell death. Functionalized GQDs can act as photosensitizers or carriers for photosensitizing agents, enabling efficient ROS production upon light activation. When exposed to specific wavelengths of light, GQDs generate reactive oxygen species, such as singlet oxygen and free radicals. These ROS cause oxidative damage to cellular components, including lipids, proteins, and DNA, leading to apoptosis or necrosis of cancer cells [52].

One of the key advantages of GQD-based PDT is its ability to provide localized treatment, as ROS generation occurs only at the irradiated site. This reduces systemic toxicity and enhances treatment precision. Furthermore, the combination of PDT with other therapeutic modalities, such as chemotherapy or PTT, can produce synergistic effects, improving overall treatment outcomes.

8.4. Theranostics-

Theranostics is an advanced approach that integrates therapeutic and diagnostic functions into a single platform. Functionalized GQDs are particularly well-suited for theranostic applications due to their intrinsic photoluminescence and drug delivery capabilities. GQDs can simultaneously serve as imaging agents and drug carriers, enabling real-time monitoring of drug delivery and therapeutic response. Their fluorescence properties allow visualization of nanoparticle distribution within the body, while their drug-loading capacity enables targeted therapy [53].

This dual functionality enhances treatment precision by allowing clinicians to track the localization of the drug and assess its effectiveness. In addition, theranostic systems based on GQDs can facilitate personalized medicine by enabling patient-specific treatment strategies.

Table 3. Recent Studies on GQD-Based Anticancer Drug Delivery

Study/ Author	Drug/ Method	Functionaliza-tion	Application	Mechanism	Key Outcome
Sun et al.	DOX-loaded GQDs	PEGylation	Targeted chemotherapy	pH-responsive release	Enhanced tumor targeting, reduced systemic toxicity
Li et al.	Paclitaxel-GQDs	Carboxylation	Drug delivery	Controlled intracellular release	Improved solubility and bioavailability

Zhang et al.	GQDs (PTT)	Surface modified GQDs	Photothermal therapy	NIR-induced heat generation	Efficient tumor ablation with minimal damage
Wang et al.	GQDs (PDT)	Photosensitizer conjugation	Photodynamic therapy	ROS generation	Enhanced cancer cell apoptosis
Chen et al.	GQD-based theranostics	Ligand conjugation	Imaging + therapy	Simultaneous diagnosis & treatment	Real-time monitoring with effective therapy
Liu et al.	DOX-GQD nanocarrier	Amination	Targeted delivery	Electrostatic interaction + pH release	Increased cellular uptake and drug efficiency
Kim et al.	GQD nanoplatform	Peptide functionalization	Tumor targeting	Receptor-mediated endocytosis	Improved targeting specificity
Singh et al.	GQDs (combined PTT + PDT)	Hybrid functionalization	Combination therapy	Heat + ROS generation	Synergistic anticancer effect
Zhao et al.	Drug-free GQDs	Surface engineered	Phototherapy	Photothermal conversion	Reduced toxicity, effective tumor suppression
Patel et al.	GQD-polymer nanocarrier	PEG + ligand	Targeted chemotherapy	Sustained drug release	Enhanced circulation time and stability

Table 4: Comparative Evaluation of GQDs with Conventional Nanocarriers

Parameter	**GQDs**	**Liposomes**	**Polymeric Nanoparticles**	**Dendrimers**
Particle Size	<10 nm (ultrasmall)	50–200 nm	100–300 nm	5–20 nm
Drug Loading	Moderate–High	High	Moderate	High
Targeting Ability	High (functionalizable)	Moderate	High	Very high
Biocompatibility	Generally high	Excellent	Good	Moderate (toxicity concerns)
Stability	High	Moderate (leakage issues)	High	High
Controlled Release	Excellent (stimuli-responsive)	Moderate	Good	Excellent
Toxicity	Dose-dependent	Low	Moderate	Higher (cationic toxicity)
Clinical Status	Preclinical	Approved	Some approved	Limited
Cost & Scalability	Challenging	Moderate	Moderate	Expensive

9. Toxicity and Biocompatibility:

The evaluation of toxicity and biocompatibility is a critical aspect in the development of graphene quantum dots (GQDs) for biomedical applications.

Although GQDs are generally considered safer compared too many metal-based nanoparticles, their interaction with biological systems must be carefully assessed to ensure clinical applicability. Factors such as particle size, surface chemistry, concentration, and functionalization significantly influence their toxicity profile. Comprehensive studies, including in vitro and in vivo evaluations, are essential to determine their safety, biodistribution, and clearance mechanisms.

9.1. In Vitro Toxicity Studies-

In vitro toxicity studies are commonly performed to assess the cytotoxic effects of GQDs on various cell lines under controlled laboratory conditions. These studies typically involve cancer cell lines (such as HeLa, MCF-7, and A549) as well as normal cell lines to evaluate both therapeutic efficacy and safety. Most studies have reported that GQDs exhibit low cytotoxicity at lower concentrations, primarily due to their small size and biocompatible carbon-based structure. Cell viability assays, such as MTT and LDH assays, indicate that GQDs maintain high cell viability, particularly when appropriately functionalized [54].

However, at higher concentrations or with certain surface modifications, GQDs may induce dose-dependent toxicity, including oxidative stress, membrane damage, and mitochondrial dysfunction. The generation of reactive oxygen species (ROS) is one of the key mechanisms responsible for cytotoxic effects, which can lead to apoptosis in both cancerous and, in some cases, normal cells [55]. Functionalization plays a crucial role in reducing toxicity by improving stability and minimizing aggregation. For instance, PEGylated or biocompatible ligand-functionalized GQDs demonstrate significantly improved cellular compatibility compared to unmodified nanoparticles.

9.2. In Vivo Studies-

In vivo studies provide valuable insights into the biological behavior, safety, and therapeutic performance of GQDs within living organisms. These studies are typically conducted using animal models such as mice or rats to evaluate parameters including toxicity, biodistribution, pharmacokinetics, and therapeutic efficacy. Experimental findings suggest that GQDs exhibit favorable biocompatibility and minimal systemic toxicity at controlled doses. After administration, GQDs are generally well tolerated, with no significant damage observed in major organs such as the liver, kidneys, heart, and lungs [56].

Histopathological analysis and blood biochemical parameters further support their safety profile, indicating minimal inflammatory response and negligible organ toxicity. However, long-term exposure studies remain limited, and there is a need for further investigation into the chronic effects and potential accumulation of GQDs in biological systems. Surface modification again plays a critical role in influencing in vivo behavior. Functionalized GQDs tend to exhibit improved circulation time, reduced immune recognition, and enhanced targeting efficiency compared to non-functionalized counterparts.

9.3. Biodistribution and Clearance-

Understanding the biodistribution and clearance of GQDs is essential for evaluating their safety and effectiveness as drug delivery systems. Biodistribution refers to the distribution of nanoparticles across different organs and tissues following administration. Studies have shown that GQDs can circulate in the bloodstream and preferentially accumulate in tumor tissues due to the enhanced permeability and retention (EPR) effect. In addition, organs such as the liver and kidneys are commonly involved in nanoparticle uptake and processing [57]. Regarding clearance, GQDs are primarily eliminated through the renal (kidney) pathway due to their small size, which allows them to pass through the glomerular filtration barrier. This rapid clearance reduces the risk of long-term accumulation and associated toxicity. In some cases, partial elimination through the hepatobiliary system has also been observed [58].

Metabolism of GQDs involves interactions with biological fluids and cellular components, which may lead to surface modifications or degradation over time. Importantly, the rate of clearance and biodistribution profile can be significantly influenced by factors such as particle size, surface charge, and functionalization. Overall, GQDs demonstrate a favorable balance between therapeutic effectiveness and safety, making them promising candidates for clinical applications. However, further long-term and large-scale studies are required to fully establish their toxicity profile and regulatory acceptance.

Table 5: Toxicological Profile of GQDs Based on Physicochemical Properties

Parameter	**Observation**	**Impact on Safety**
Size (<10 nm)	High cellular penetration	Potential systemic distribution
Surface Charge (+ve)	Higher uptake	Increased cytotoxicity
Surface Functionalization	PEG reduces toxicity	Improves biocompatibility
Dose	High dose → ROS generation	Oxidative stress risk

Exposure Time	Long-term accumulation	Unknown chronic effects
Biodistribution	Liver/kidney accumulation	Clearance concerns

10. Challenges and Limitations:

Despite the promising potential of functionalized graphene quantum dots (GQDs) in drug delivery and cancer therapy, several challenges and limitations must be addressed before their successful clinical translation. One of the primary concerns is large-scale production. Although various synthesis methods have been developed, achieving consistent, high-yield, and reproducible production of GQDs with uniform size and properties remains challenging. Many existing methods either lack scalability or involve complex procedures and expensive equipment, which limits their industrial applicability [59].

Another significant issue is toxicity concerns. While GQDs are generally considered biocompatible, their toxicity profile can vary depending on factors such as size, surface functionalization, concentration, and exposure duration. Some studies have reported oxidative stress and cellular damage at higher concentrations, highlighting the need for comprehensive long-term toxicity evaluations [60]. Regulatory issues also present a major barrier to the clinical use of GQDs. The lack of standardized guidelines for the characterization, safety evaluation, and approval of nanomaterials complicates the regulatory process. Regulatory agencies require extensive data on pharmacokinetics, toxicity, and environmental impact, which is currently limited for GQDs [61].

Furthermore, clinical translation barriers remain a critical challenge. Although numerous in vitro and in vivo studies have demonstrated the effectiveness of GQDs, there is a significant gap between laboratory research and clinical application. Factors such as large-scale manufacturing, reproducibility, long-term safety, and cost-effectiveness must be addressed to facilitate their transition into clinical practice.

11. Future Perspectives:

The future of functionalized graphene quantum dots in nanomedicine is highly promising, with ongoing research focusing on overcoming current limitations and expanding their applications in cancer therapy. One of the key areas of development is the design of multifunctional nanocarriers. Future GQD-based systems are expected to integrate multiple functionalities, such as drug delivery, imaging, and therapeutic action (e.g., photothermal and photodynamic therapy), within a single platform. These multifunctional systems can enhance treatment efficiency and enable combination therapies for improved clinical outcomes [62].

Another emerging trend is personalized nanomedicine, where GQDs can be tailored to meet the specific needs of individual patients. By incorporating patient-specific biomarkers and targeting ligands, GQD-based systems can provide more precise and effective treatments, minimizing adverse effects and improving therapeutic success rates [63]. Advancements in clinical applications are also anticipated as more preclinical studies progress toward clinical trials. With improved safety profiles and optimized functionalization strategies, GQDs have the potential to become integral components of next-generation cancer therapies.

Additionally, the integration of artificial intelligence (AI) in nanomedicine design is expected to revolutionize the development of GQD-based systems. AI can assist in predicting nanoparticle behavior, optimizing drug loading and release profiles, and accelerating the design of efficient nanocarriers. This data-driven approach can significantly reduce development time and improve the precision of nanomedicine [64].

12. Critical Analysis and Research Gaps:

12.1 Critical Analysis-

Despite the rapid advancement of graphene quantum dots (GQDs) in drug delivery and cancer theranostics, a critical evaluation of the current literature reveals several fundamental limitations that hinder their clinical translation.

One of the most prominent concerns is the lack of standardization in synthesis protocols, which leads to significant variability in particle size, surface chemistry, and functional group distribution. Studies employing top-down and bottom-up approaches often report inconsistent physicochemical characteristics, making it difficult to establish reproducibility and cross-comparison between different research findings. This variability directly affects biological performance, including cellular uptake, biodistribution, and therapeutic efficacy.

Another key limitation lies in the predominantly in vitro nature of existing studies. While many reports demonstrate enhanced drug loading, targeted delivery, and controlled release behavior, these outcomes are largely confined to simplified laboratory conditions. The translation of such results into complex in vivo systems remains uncertain, particularly due to biological barriers such as protein corona formation, immune clearance, and tumor heterogeneity. Consequently, the therapeutic performance observed in preclinical studies may not accurately reflect clinical outcomes.

The issue of toxicity and long-term safety remains inadequately addressed. Although GQDs are generally

considered biocompatible, emerging evidence suggests that their toxicity is highly dependent on dose, size, and surface functionalization. In particular, the generation of reactive oxygen species (ROS) can induce oxidative stress, mitochondrial dysfunction, and unintended damage to healthy tissues. Moreover, there is a significant lack of long-term in vivo studies evaluating chronic exposure, accumulation, and potential genotoxic effects.

From a therapeutic perspective, while stimuli-responsive drug release systems (e.g., pH, redox, enzyme-triggered) have shown promising results, their real-world applicability is limited by the heterogeneity of tumor microenvironments. Variations in pH gradients, enzyme expression levels, and intracellular conditions across different tumor types can lead to inconsistent drug release profiles, thereby reducing treatment efficacy.

Furthermore, although GQDs exhibit excellent potential in photothermal and photodynamic therapies, these approaches are constrained by limited tissue penetration of light, particularly in deep-seated tumors. This significantly restricts their applicability to superficial or accessible cancers, limiting their broader clinical utility.

Another critical gap is the lack of quantitative comparative studies. Most research reports focus on individual systems without benchmarking against established nanocarriers such as liposomes, polymeric nanoparticles, or dendrimers. As a result, it remains unclear whether GQDs offer a substantial clinical advantage over existing delivery platforms in terms of efficiency, safety, and cost-effectiveness.

Finally, challenges related to scalability and manufacturing reproducibility continue to impede industrial translation. Many synthesis methods involve complex procedures, expensive instrumentation, or low yield, making large-scale production economically unfeasible. In addition, the absence of well-defined regulatory guidelines for carbon-based nanomaterials further complicates their progression toward clinical approval.

Overall, while functionalized GQDs represent a highly promising nano platform, their successful translation into clinical practice will depend on addressing these critical challenges through standardized synthesis, robust in vivo validation, and systematic comparative evaluation.

12.2 Research Gaps-

Despite extensive research on functionalized GQDs, several gaps remain that must be addressed to enable their successful clinical translation. One of the major gaps is the lack of long-term toxicity and safety studies. Most available research focuses on short-term evaluations, while the long-term effects, accumulation, metabolism, and potential chronic toxicity of GQDs in the human body are still not fully understood.

Another significant gap is the absence of standardized synthesis and characterization protocols. Variations in preparation methods lead to inconsistencies in physicochemical properties, making it difficult to compare results across studies or develop reproducible formulations for large-scale applications. There is also limited research on pharmacokinetics and biodistribution in humans. Although animal studies suggest renal clearance and tumor accumulation, these findings may not directly translate to human physiology. More advanced and clinically relevant models are required to bridge this gap.

Furthermore, clinical trials involving GQDs are extremely limited, highlighting a major disconnect between experimental research and real-world medical application. Regulatory challenges further complicate this issue, as there are no well-defined guidelines specifically tailored for carbon-based nanomaterials. Another overlooked area is the interaction of GQDs with the immune system. Understanding immunogenic responses is crucial for ensuring safety, especially for repeated or long-term therapeutic use.

Lastly, while multifunctional and theranostic systems are being explored, there is still insufficient research on cost-effectiveness, scalability, and commercial feasibility, which are essential for translating these technologies from laboratory research to clinical practice. Addressing these research gaps will be critical for advancing GQDs from promising nanomaterials to clinically approved and widely used therapeutic platforms.

13. Conclusion:

In summary, functionalized graphene quantum dots represent a highly promising class of nanomaterials with significant potential in drug delivery and cancer therapy. Their unique structural features, combined with versatile surface functionalization, enable efficient drug loading, targeted delivery, and controlled release of therapeutic agents. The integration of GQDs into cancer treatment strategies has demonstrated notable advantages, including improved targeting capability, reduced systemic toxicity, and enhanced therapeutic efficacy. Furthermore, their applications in photothermal therapy, photodynamic therapy, and theranostics highlight their multifunctional nature and potential to revolutionize cancer treatment. Despite these advancements, challenges related to large-scale production, toxicity, regulatory approval, and clinical translation must be addressed. Continued research efforts are essential to overcome these limitations and to fully realize the clinical potential of GQDs. Future developments in multifunctional nanocarriers,

personalized medicine, and AI-assisted design are expected to further enhance the capabilities of GQD-based systems. With ongoing innovation and interdisciplinary collaboration, functionalized graphene quantum dots hold great promise for advancing targeted cancer therapy and improving patient outcomes.

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