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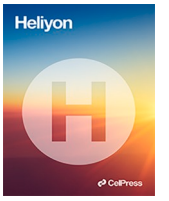

Review article

A holistic review on red fluorescent graphene quantum dots, its synthesis, unique properties with emphasis on biomedical applications

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ABSTRACT

Graphene quantum dots (GQDs) are an evolving class of carbon-based nanomaterial, seizing tremendous attention owing to their intense optical property, engineered shapes and structures, and good photostability. Being a zero-dimensional form of carbon structure, GQDs have superior photoluminescent behavior, tunable emission and absorption, excellent biocompatibility, low cytotoxicity, hydrophilic nature, modifying surface states. Their water dispersibility and functionalized surface structure, involving heteroatoms and various functional groups onto the surface of GQDs, make them particularly suitable for biological applications. Based on their absolute luminescence properties, GQDs emit blue, green, yellow, and red light under ultraviolet irradiation. Amongst the three colors, red luminescence can achieve deeper penetration of light into tissues, good cellular distribution, bio-sensing property, cell imaging, drug delivery, and serves as a better candidate for photodynamic therapy. The overall objective of this review is to provide a comprehensive overview of the synthesis methods for red fluorescence graphene quantum dots (RF-GQDs), critical comparative analyses of spectral techniques used for their characterization, the tunable photoluminescence mechanisms underpinning red emission, and the significance of chemically functionalizing GQDs' surface edges in achieving red fluorescence are discussed in depth. This review also discusses the effective biological applications and critical challenges associated with RF-GQDs are examined, providing insights into their future potential in clinical and industrial applications.

1. Introduction

The 1980s witnessed the discovery of semiconductor nanocrystals, such as cadmium sulfide (CdS) and cadmium selenide (CdSe), which display unique optical and electrical properties because of quantum confinement phenomena. This marked the beginning of the history of quantum dots [1]. A notable breakthrough was made in the early 2000s with the development of Carbon Quantum Dots (CQDs), which are tiny quasi-spherical carbon particles, discovered by the electrophoretic fragmentation of single-walled carbon nanotube, which were later recognized as CQDs [1,2].

Another significant achievement was the 2004 discovery of graphene, which is a carbon-based nanomaterial. Graphene is the most

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Abbreviations

(CH)n	Graphane
2D	Two-dimensional
ABTS	2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)
DBM	Dibenzoylmethane
DI	Deionized water
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Eu(III)	Europium trivalent ion
FTIR	Fourier transform infrared spectroscopy
FWHM	Full width at high maximum
GO	Graphite oxide
GQDs	Graphene quantum dots
GQDs-NHR	Alkyl amine-functionalized graphene quantum dots
H_2O_2	Hydrogen peroxide
H_2SO_4	Sulfuric acid
HCL	Hydrochloric acid
HNO_3	Nitric acid
HOMO	Highest occupied molecular orbital
HRTEM	High-resolution transmission electron microscopy
$K_2S_2O_8$	Potassium persulfate
$KMnO_4$	Potassium permanganate
LEDs	Light-emitting diodes
LUMO	Lowest unoccupied molecular orbital
MAH	Microwave-assisted hydrothermal method
MCF-GQDs	Multicolor fluorescent graphene quantum dots
$NaNO_3$	Sodium nitrate
NaOH	Sodium hydroxide
N-GQDs	Nitrogen-doped graphene quantum dots
NH_4OH	Ammonium hydroxide
NIR	Near-Infrared
PDT	Photodynamic therapy
PEG	Polyethylene glycol
PEI	Polyethyleneimine
Phen	1, 10-phenanthroline
PL	Photoluminescence
PLE	Photoluminescence spectra
PpIX	Protoporphyrin IX
PSs	Photosensitizer
PT2	Polythiophene
PTT	Photothermal therapy
QY	Quantum yield
RF-GQDs	Red fluorescent graphene quantum dots
rGO	Reduced graphene oxide
R-GQDs	Red graphene quantum dots
RhB	Rhodamine B
ROS	Reactive oxygen species
S, N- GQDs	Sulfur and nitrogen co-doped graphene quantum dots
TBAP	Tetrabutylammonium perchlorate
TEM	Transmission electron microscopy
TiO_2	Titanium dioxide
TPPL	Two-photo photoluminescence
UV	Ultraviolet irradiation
UV–vis	Ultraviolet–visible spectrophotometer
XPS	X-ray photoelectron spectroscopy

recently discovered carbon-based nanomaterial, constructed with carbon atoms within a structured pattern in the form of a single layered, two-dimensional (2D) (each atom is one layer thick) hexagonal honeycomb lattice of sp^2 hybridization [3]. Graphene is the strongest, stiffest, thinnest, and most flexible compound with exclusive electrical, thermal, mechanical, and physiochemical properties and has been extensively applied in various fields [4–6]. Subsequently, the derivatives of graphene-based materials include reduced graphene oxide (rGO), graphene oxide (GO), graphane (CH)n, graphone (hydrogenated form of graphene), graphyne (with one acetylene linkage in the carbon lattice), graphdiyne (has two acetylenic bonds in one unit cell), and graphene quantum dots (GQDs) [7].

This finding sparked significant research into their synthesis, characteristics, and applications, ultimately leading to the production of Graphene Quantum Dots (GQDs) in 2008 [8]. Carbon Quantum Dots (CQDs) and Graphene Quantum Dots (GQDs) are two distinct types of zero-dimensional carbon nanomaterials with unique structural and functional properties owing to their nanoscale dimensions. CQDs are small spherical carbon particles smaller than 10 nm in diameter, largely consisting of sp^2-and sp^3-hybridized carbon atoms, with a more amorphous and disordered structural core [9].

GQDs are two-dimensional nanocrystals composed of tiny graphene particles with lateral dimensions less than 100 nm. They have a crystalline sp2 carbon nanosheet structure [9]. CQDs have a more disordered core than GQDs owing to the differences in thickness and crystalline states, which influence their distinct characteristics and uses [10]. Filtering out CQDs and GQDs with excessive thickness or ambiguous crystalline states is critical for ensuring optimum performance because these characteristics may adversely affect their distinctive electrical and optical properties. GQDs feature a higher degree of crystallinity and a more ordered arrangement of carbon atoms, which lead to increased quantum yield and photoluminescence efficiency [11]. In contrast, CQD's disordered structure of CQDs leads to a lower quantum yield and less efficient photoluminescence than GQDs [12].

Owing to their crystalline nature, the focus shifted to emphasizing the superior attributes of the GQDs on their luminescence. The bandgap of GQDs can be tuned by modifying their size or surface edge states, which are associated with their remarkable luminescence. The photoluminescence (PL) behavior of GQDs depends on the size, quantum confinement of π-domains, and surface functional groups, which influence the fluorescence properties in the blue to red light region [13,14]. Compared to traditional quantum dots, fluorescent GQDs display many advantages, such as good biocompatibility, low cytotoxicity, good water solubility, and excellent luminescent properties [15]. Among the different color emission and fluorescence properties, red fluorescence has gained attention owing to its unique properties of deeper light penetration with long-wavelength emission, better photostability, and high quantum yield [16,17], which can be extensively applied in fields such as photodynamic therapy, where red emission increases tissue penetration for cancer therapy [18], biosensing probes, cellular imaging, and drug delivery. Furthermore, red fluorescence enables cell labelling and monitoring of live cells in a biological system [19]. However, owing to these unique properties, only a few methods have been reported for the synthesis of red-fluorescence graphene quantum dots (RF-GQDs) [20,21]. Previously, for the synthesis of GQDs, two main approaches have been adopted: bottom-up and top-down. In this review, the synthesis methods used by various researchers to prepare RF-GQDs has been summarized. It includes both methods, as bottom-up methods refer to the use of graphene oxide (GO), graphite powder, carbon black, and glucose, and ammonia is used as a carbon and nitrogen source that is further converted to GQDs by a series of chemical reactions. In the top-down method, a graphite rod is used, which is eventually exfoliated to GQDs [22–24]. The list of desired methods used for preparing RF-GQDs are hummers method which is a potent oxidation process that involves strong oxidant chemicals, electrochemical exfoliation method, solvothermal, and microwave-assisted hydrothermal comprising top-down approach, which is a comparatively simple, fast, effective, and commonly used method. The bottom-up approach includes pyrolysis, the hydrothermal method, and the one-pot method, which uses organic precursors to prepare GQDs by controlling their size and morphology [25,26].

In addition, various techniques have been used to characterize GQDs. High-resolution transmission electron microscopy (HRTEM) observations reveal that the GQDs have a crystalline structure and interplanar spacing of 0.24 nm like the lattice fringes of graphite [17]. X-ray photoelectron spectroscopy (XPS) and Fourier transform infrared spectroscopy (FTIR) were performed to study the chemical composition of the GQDs and demonstrate the carbon and oxygen spectra, confirming the presence of oxygen-containing functional groups, including hydroxyl, carboxyl, carbonyl, and epoxy groups [20]. The UV–visible absorption and photoluminescence spectra (PLE) exhibit broad absorption spectra and luminescent properties of GQDs, respectively. GQDs have a π-π* transition absorption peak, which generally ranges from to 200–270 nm and a shoulder peak above 260 nm with an n-π* transition attributed to functional groups on the surface. The PLE spectra define the excitation and emission properties of GQDs [6,27,28]. Raman spectroscopy is used to study the defective structure of graphene with characteristic D and G band [29,30].

One of the most important properties of GQDs is PL tunability, which exhibits a redshift by tuning the band gap, followed by a fluorescence mechanism displaying two behaviors: excitation-dependent [31] and excitation-independent emission based on the surface states by functionalization or element doping to enhance the fluorescence efficiency [32]. Functionalization of GQDs with functional groups such as hydroxyl and carboxyl groups modulate their properties, providing a hydrophilic nature, sufficient π-π conjugation, large surface area, and efficient tuning of surface edges to a biological system [33,34]. The functionalization and chemical doping of GQDs with nitrogen and sulfur also influence the quantum yield by tuning their optical properties [35,36]. By improving these properties, RF-GQDs can potentially be applied in various fields such as deep tissue imaging, biosensing, cancer therapy bio-labelling, and fluorescence imaging because of their good photostability and resistance to photobleaching [28,37,38].

Despite, numerous review articles outlining the new synthetic techniques to synthesize various carbon dots, exclusively graphene quantum dots with superior optical characteristics of electrochemiluminescence and photoluminescence; almost fewer insights have been focused on key factors influencing PL shift to red/near-infrared emission aspiring to be a potential agent in the biomedical domain. Herein, a detailed overview of the synthesis of red fluorescent graphene quantum dots, its diverse properties, and biomedical applications has been reported. In a nutshell, this review effectively outlines multicolor emission, PL mechanism, and specific

mechanism needed for synthesizing RF-GQDs and briefing the strategies adapted for synthesizing RF-GQDs with different source materials and detailing its comprehensive analysis for scaling up, then comparing spectroscopic techniques for potential GQDs. Then concentrated on RF-GQD's unique properties- PL tunability alongside the mechanism enabling red emission, mechanism of fluorescence with the property of excitation-emission, functionalization process, and directions of quantum yield for red emission. Furthermore, the biomedical applications of RF-GQDs such as photodynamic therapy (PDT), bio-imaging, bio-probes, and a few other applications, and emphasize a few experimental findings of RF-GQDs with highlights on regulatory approval for clinical translation were discussed. In addition, the review also addresses potential challenges and limitations that impact the red fluorescence quantum dots efficiency, potential feasibility for industrial application, and insights on clinical implementations.

Finally, the review highlighted the potential outcomes and shortcomings of RF-GQDs. Certainly, the explicative insights and viewpoints provided in this review will encourage new and interesting studies on R/NIR- GQDs material characteristics and synergetic biological application.

2. Historical overview of multicolor emitting graphene quantum dots (GQDs)

Graphene Quantum Dots (GQDs) have emerged as an intriguing class of materials due to their tunable photoluminescent (PL) properties which cover the visible and near-infrared (NIR) spectrums. This historical review follows the evolution of GQD synthesis from blue to red emission, emphasizing the technological developments that enabled these advancements in multicolor emission [39].

2.1. Blue emission GQDs- early 2000s

The discovery of blue-emitting GQDs initiated the first phase of GQD research. Usually, top-down techniques like oxidative cutting and hydrothermal treatment of graphene oxide (GO) were used to create these GQDs. The blue emission was mostly ascribed to the electronic transitions in the GQDs that were influenced by the presence of oxygen-containing groups on their surface [40], specifically the π-π* (transition of sp^2 domain), $n_{O\ 2p}$-π* (transition of protonation -COO^-), and $n_{N\ 2p}$-π* (transition of amino group) ones, as well as the quantum confinement effect [41]. GQDs' intense blue fluorescence and superior biocompatibility were highlighted in important research showing their potential for bioimaging and optoelectronic applications [40,41].

2.2. Green emission GQDs- late 2000s - early 2010s

As research proceeded, the emphasis shifted to synthesizing green emissions from GQDs. This was achieved by fine-tuning the synthesis protocols to better regulate the size, surface states, and functional groups [42]. The green emission from GQDs is attributed to the π-π* (transition of sp^2 domain), $n_{O\ 2p}$-π* (transition of protonation and deprotonation of -COO^-), and mainly $n_{N\ 2p}$-π* (transition of amino group) electronic transitions, which are impacted by the presence of functional groups such as amino, carboxyl, and ammonium carboxylate groups on the GQD surface [41]. To modify the emission parameters of green-emitting GQDs, further procedures such as chemical reduction and passivation were frequently used [43].

2.3. Yellow and orange emission GQDs- mid 2010s

Not too long after the first reports of blue and green emissions, yellow and orange emissions from GQDs were discovered. The controlled synthesis of GQDs with particular functional groups and surface states-nitrogen doping was another method used to produce

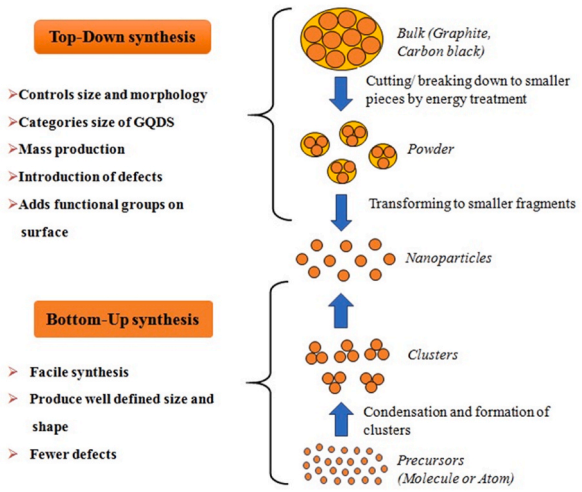

Fig. 1. Schematic illustration of two main typical approaches adapted for GQDs synthesis.

these emissions [44]. Even more precise control over the synthesis process was needed to increase the emission wavelength to obtain yellow and orange emission [41]. Researchers started experimenting with various precursor materials and synthesis conditions, such as altering the GQDs' size and form, adding specified functional groups, and altering the degree of oxidation [45].

2.4. Red emission GQDs- late 2010s - present

Red emission from GQDs was discovered considerably later than blue and green. The development of red-emitting GQDs was hampered by the requirement for precise control over structural and electronic properties [46]. In 2017, *o*-phenylenediamine and catechol were used as precursors to create red-emission GQDs (R-GQDs), one of the first reports of red-emitting GQDs. High-quality red-emitting GQDs have been produced by applying technologies such as microwave-assisted synthesis, electrochemical exfoliation, and laser ablation. The presence of several nitrogen species (pyrrolic N, pyridinic N, and amino N) on the surface of R-GQDs was responsible for the red emission, allowing for triple fluorescence emissions. A smaller bandgap is needed for red emission, and this can be accomplished by developing GQDs with specific functionalization and fewer defects [47].

2.5. Photoluminescence (PL) mechanism of red fluorescent GQDs

The PL mechanism of red fluorescent GQDs (R-GQDs) involves several key factors:

Quantum Confinement Effect: Graphene Quantum Dots (GQDs) display a quantum confinement phenomenon, in which the electronic bandgap increases as the quantum dots' size decreases, causing shifts in emission wavelengths [48]. Blue and green GQDs are typically smaller, resulting in broader bandgaps and shorter wavelength emissions. In contrast, red-emitting GQDs are often bigger, narrowing the bandgap and allowing for longer-wavelength emissions [49]. Precise control over the size of GQDs is critical for fine-tuning photoluminescent (PL) characteristics by quantum confinement [48].

Surface Functional Groups: Surface functional groups are critical in determining the PL characteristics of GQDs. Specific functional groups, such as carboxyl, hydroxyl, and amino groups, introduce new electronic states into the bandgap. These functional groups have the ability to alter the electronic structure of GQDs, allowing for red emission through the formation of new emissive states. Proper functionalization improves not only the PL characteristics but also the chemical stability and solubility of GQDs [48].

Edge States: Edge state configuration has a substantial impact on GQD's electrical and PL properties. GQDs involve multiple edge configurations, particularly zigzag and armchair edges, which contribute differentially to the electronic states [50]. Longer wavelength emission can be supported by creating energy levels through proper engineering of these edge states [51]. For example, zigzag edges might introduce localized states that allow red emission, but armchair edges affect overall PL efficiency and stability. The surface state includes triplet carbenes at the zigzag edges, attached chemical groups, surface defects, heteroatom doping in the carbon lattice, and the gigantic red-edge effect [50,52].

Defect States: To achieve red emission in GQDs, controlled defect introduction and passivation are crucial. New emissive centers are produced by defects that lead to localized electronic states within the bandgap. However, excessive defects can quench PL, making it critical to achieve a balance. To introduce the proper defect density, type and improved red emission without sacrificing PL efficiency, meticulous control over the synthesis process is necessary [50,52].

Size and Shape: The PL mechanism may also be influenced by the GQDs' size and shape. The quantum confinement effect and the surface/edge state can be influenced by the shape and size of the GQDs, which can modify the PL characteristics [52].

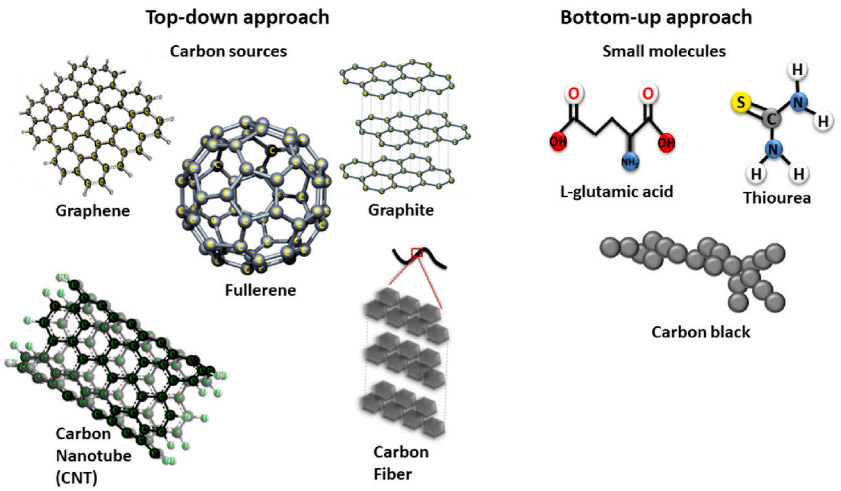

Fig. 2. A brief overview of the sources used for Red fluorescent graphene quantum dots based on top-down and bottom-up strategy.

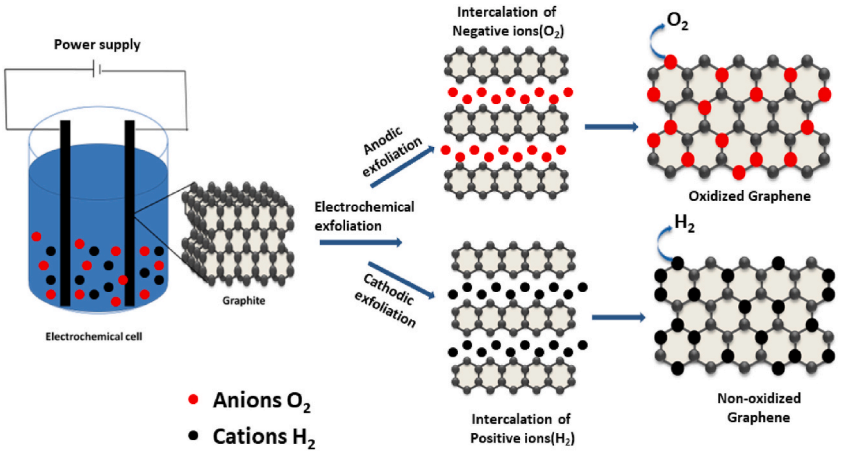

Fig. 3. Synthesis of graphene quantum dots via electrochemical exfoliation method.

2.6. *Specific conditions for RF-GQDs synthesis*

RF-GQDs (Red Fluorescent Graphene Quantum Dots) are synthesized differently than blue and green GQDs using a combination of distinct chemical and physical techniques designed to produce the required red emission attributes. Chemically, RF-GQDs are frequently synthesized with particular precursors such as graphene oxide (GO) and nitrogen-containing chemicals such as ammonia or amines, which introduce functional groups that aid in red emission by electrochemical synthesis [53]. Physical methods such as microwave irradiation, ultrasonication, or solvothermal treatment are employed for reducing larger graphene materials to smaller GQDs with controlled size, shape, and surface functionalization [54]. Furthermore, hybrid synthesis methods, which combine chemical precursors (GO) and physical approaches (microwave), enable exquisite control over the properties of RF-GQDs. The choice of precursor, reaction conditions, and physical methods like temperature, time, and solvent type, used can influence the properties of the GQDs produced to achieve red fluorescence, and the use of hybrid synthesis methods can lead to the formation of GQDs with specific properties [53].

2.7. *Significance of studying RF-GQDs compared to other luminescent GQD*

The research of Red Fluorescent Graphene Quantum Dots (RF-GQDs) is far more significant than that of other luminous GQDs due to their distinct features and potential applications. Because of their high quantum yield, long fluorescence duration, and narrow emission band, RF-GQDs are perfect for a wide range of optoelectronic and biological uses. Featuring their distinct red fluorescence emission, RF-GQDs stand out from other luminous GQDs, this characteristic makes them less vulnerable to interference from other biological molecules and enables more accurate imaging and detection [55]. Furthermore, RF-GQDs have been demonstrated to display superior biocompatibility, tunability, and biodegradability compared to other luminous GQDs, which makes them more appropriate for in vivo applications. Moreover, RF-GQDs are more feasible for practical application because it has been shown that they have a longer shelf life and higher stability than other luminous GQDs. Due to their unique properties and potential uses in

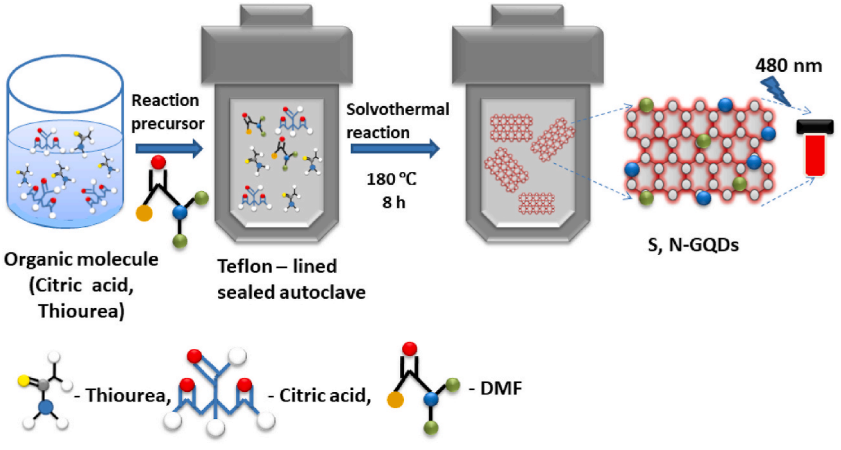

Fig. 4. Synthesis of co-doped graphene quantum dots with strong emission using solvothermal method.

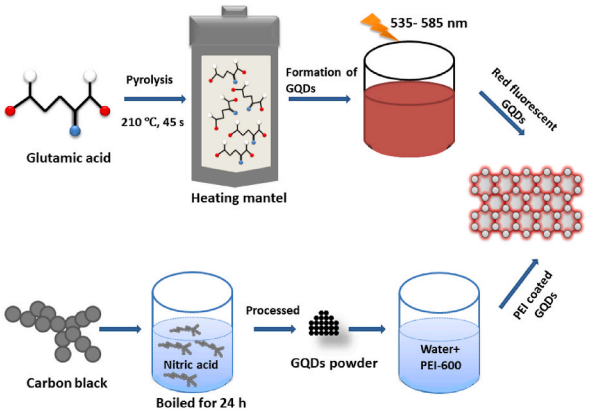

Fig. 5. Pyrolysis technique was employed to prepare fluorescent graphene quantum dots by utilizing carbon source materials.

bioimaging, optoelectronics, and cancer treatment, RF-GQDs are a promising field for future research [56].

3. Synthesis of RF- GQDs

Usually, GQDs synthesis can be categorized into two ways; either top-down or bottom-up approach as shown in Fig. 1 [57–59]. Many methods are available for the synthesis of GQDs in which few methods are focused on synthesizing RF- GQDs by controlling their size and quality of the synthesized material. Fig. 2 depicts the summary of synthetic materials available for synthesizing RF-GQDs via two critical strategies [60].

3.1. Electrochemical exfoliation method

Electrochemical exfoliation is a simple method that proceeds to intercalation between graphite to form separate layers, when voltage is passed through the graphitic electrode hydrolysis of water takes place, giving H^+ and OH^- ions acting as electrochemical scissors to cut the separated layers of graphene into GQDs [15,61]. Potential play's important role in the intercalation of ions, when the potential is positive its anodic exfoliation if its negative then cathodic exfoliation [35], the procedure is shown in Fig. 3 [62–64].

The electrochemical setup usually contains graphite as a working electrode and counter electrode immersed completely into the electrolyte solution for proper exfoliation [65]. Recently, Tan et al. synthesized uniform-sized RF- GQDs by electrochemical exfoliation of graphite in 0.01 M $K_2S_2O_8$ as an electrolyte solution. The synthesized RF- GQDs are water-soluble and 3 nm in size especially without any chemical modification. The water-soluble RF- GQDs are further applied for cellular imaging of HeLa cells providing less cytotoxicity and good photostability [66]. Liu et al. stepped forward to prepare GQDs by exfoliation of a graphite rod in a 5 ml DMSO solution containing 0.01 M TBP as an electrolyte. To increase the water solubility graphene quantum dot-europium (III) complex, has been non-covalently connected to chelating ligands like dibenzoylmethane (DBM) and 1,10- phenanthroline (phen). The obtained complex composites achieved red fluorescence with good water stability, high color purity, and a high quantum yield of 15.5 % and further used in bioimaging platform [67]. Yuan et al. reported the synthesis of temperature and pH-responsive fluorescent graphene quantum dots with red fluorescence. These GQDs were water-soluble and stable in all pH conditions, and in strongly alkaline conditions new quinone structures were being transformed from lactone giving new novel red fluorescence. Electrochemical preparation

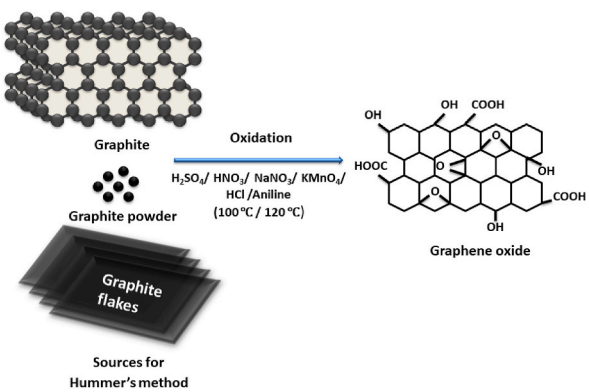

Fig. 6. Fabrication of graphene oxide via hummer's method using graphite as a precursor.

of thin and small-sized graphene from the graphite rod was prepared by dipping the graphite rod in a solution containing 0.01 M tetrabutylammonium perchlorate (TBAP) in 5 ml dimethylsulfoxide (DMSO) with current 10 mA for 3 h. At the end of the reaction, the black suspension has resulted, and it was washed with ethanol and centrifuged repeatedly to remove excess TBAP and DMSO. The GQDs was dried in an oven and slow addition of concentrated sulfuric acid and nitric acid followed by heating and stirred and condensed. After the complete process of neutralizing by sodium carbonate, the supernatant collected which contained multicolor fluorescent GQDs (MCF GQDs). HeLa cells were used to analyze the imaging ability of MCF GQDs in cells at different temperatures and pH, thus establishing its dual-sensing ability and bioimaging property [68].

3.2. Solvothermal method

A solvothermal method is one of the methods in the top-down approach of synthesis of GQDs; it is a simple method for the preparation of GQDs by controlling the size and morphology of the material, additionally solvothermal reaction's temperature and duration primarily modulates multicolor fluorescence in GQDs [69]. The solvothermal process takes place in a closed container influencing high temperature and high pressure, where the temperature of the solvent exceeds the boiling temperature of the solvent and increases in pressure. This process depends on three main factors temperature, pressure, and pH [70,71]. High temperature and high pressure can cut the large-sized carbon material (graphite) into small-sized GQDs with an oxygen-containing functional group on the surface. In general, the carbon material has to be mixed with strong acids for oxidation before the reaction happens [13]. Qu et al. developed S, N co-doped graphene quantum dots by a solvothermal method using 1 mM of citric acid and 3 mM of thiourea as carbon and N, S source respectively dissolved in 4 ml of DMF solution, the procedure depicted in Fig. 4 [72–74].

The solution was then transferred into 20 ml Teflon-lined sealed autoclave heated to 180 °C for 8 h. The prepared S, N- GQDs showed three-color emission blue, green, and red with an emission peak at 640 nm excitation wavelength ranging between 560 and 620 nm. As synthesized red-emitting S, N co-doped graphene quantum dots are used to demonstrate live imaging and detecting viability of A549 cells incubated with S, N- GQDs, furthermore attaining good bioimaging ability [75].

3.3. Pyrolysis

Pyrolysis is one of the easiest and simplest methods [76] in the bottom-up approach for the synthesis of graphene quantum dots. Pyrolysis is a thermochemical treatment that uses organic (carbon-based material) precursor for synthesizing GQDs [77]. Pyrolysis relates to thermal treatment or irreversible thermal decomposition of organic precursors, during pyrolysis, the organic material is exposed to high temperature in the absence of oxygen leading to decomposition of the material and influencing change in chemical and physical nature of the bonds in a molecule to form a different material. Mostly, in pyrolysis changing the nature of organic molecules tends to form carbon as a residue, and it's also called as carbonization [78]. Wu et al. synthesized highly fluorescent graphene quantum dots by a one-step pyrolysis method using 2 g of L-glutamic acid heated to 210 °C in a heating mantel, as shown in Fig. 5 [79–81].

The colorless, solid L-glutamic acid changes to a liquid and appears in brown insisting on the formation of GQDs. The developed GQDs showed fluorescence properties, upon irradiation with light (535–585 nm) emitted red fluorescence when investigated using a fluorescence microscope and NIR fluorescence also emitted in the range of 800–850 nm. Furthermore, GQDs were also used in *in-vitro* imaging of MH-S cells incubating with GQDs. Upon different excitation wavelength GQDs emitted strong red fluorescence when excited at 514 nm. Thus, the so-prepared GQDs could penetrate the cells and used for labeling cell membrane and cytoplasm of MH-S cells also attaining fluorescence imaging property [82]. Gao et al. synthesized red-emitting GQDs coated with polyethyleneimine (PEI) by low-temperature pyrolysis, 0.4 g of VCX-72 carbon black boiled in 100 ml nitric acid, the cooled solution was sonicated, centrifuged and the supernatant was filtered and evaporated using a rotary evaporator to remove acids. After lyophilization of the dried sample, GQDs powder was obtained. GQDs powders were then re-dissolved in water with PEI to obtain PEI-coated GQDs. PEI_{600} GQDs could emit red fluorescence when excited with 500–650 nm. The synthesized PEI_{600} GQDs incubated with human kidney cell line 293 (HEK-293) and human primary glioblastoma cell line 87 (U-87) for cell viability study, the studies showed no cell reduction exhibiting biocompatibility, less cytotoxicity and used as a good bioimaging agent in biomedical field [83].

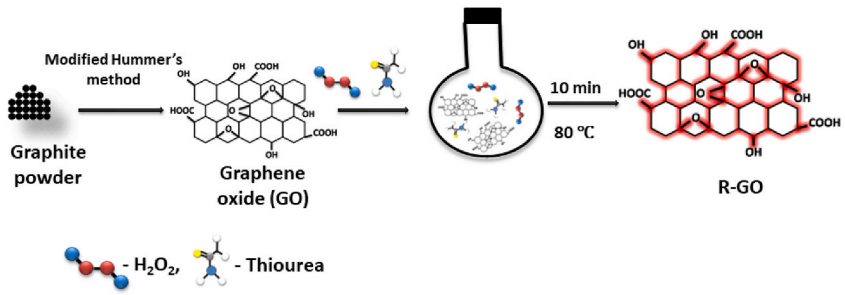

Fig. 7. Formation of red emissive graphene oxide from graphite powder by scalable one pot method.

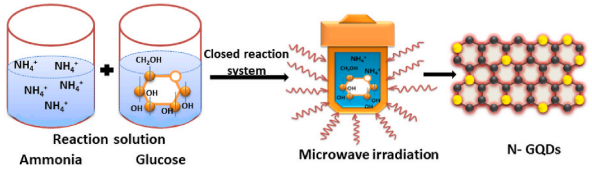

Fig. 8. Fabricating stratified N-GQDs with microwave-assisted hydrothermal method.

3.4. Hummers' method

Hummers' method is the usual chemical method and the most common approach used for the synthesis of graphite oxide (GO), in which chemical reduction of GO can easily be transformed into graphene [84]. This method can efficiently increase oxidation and it can also be another possible oxidation method [85]. Hummers' method usually uses strong oxidants like sulfuric acid, potassium permanganate, and sodium nitrate in less dose [86], the scheme of the procedure is shown in Fig. 6 [87–89].

Chhabra et al. stepped to synthesize multicolor graphene quantum dots emitting red light under UV irradiation. Graphene oxide has been prepared by using a modified Hummers' method with 55 ml of 98 % sulfuric acid and 1.0 g of graphite flakes mixed in an ice bath and 5.5 g potassium permanganate was slowly added and stirred. The solution was heated for different temperatures at different times by adding H_2O_2 and HCL and finally separating graphene oxide followed by pH adjusting and dialyzing. The obtained graphene oxide was used for the synthesis of red GQDs (R-GQDs), prior prepared GO of 5 ml mixed with 5 ml of 40 % H_2O_2 and 0.26 g aniline, this reaction mixture was heated for 10 min at 120 °C. The solution was then cooled, filtered, and dialyzed; the resulted supernatant contains fluorescent R-GQDs. The prepared R-GQDs showed excitation dependent photoluminescence with an emission peak at 558 and 648 nm obtaining good photoluminescence [90]. Kwon et al. synthesized chemically functionalized graphene quantum dots (GQDs) with series of aniline derivatives to generate a narrow linewidth of photoluminescence. The conjugation of aniline with GQDs helped to form proper energy gaps to show red photoluminescence. In this process, the bare GQDs were prepared using the Hummers' method, ~20 μm of 100 mg graphite powder, and 40 ml concentrated nitric acid was heated in a round bottom flask at 100 °C for 12 h. The resulted solution was filtered by adding excess water and 1 ml oleylamine and 9 ml 1-octadecene was added to the filtered solution and heated at 250 °C for 3 h under stirring condition. After the solution was cooled to 100 °C, 2 ml hydrazine hydrate was added and stirred for 3 h, 30 ml methanol used to precipitate the resulted dark-brown solution and centrifuged and again re-dispersed in 3 ml hexane this process was repeated three times. Using a rotary evaporator and vacuum oven the purified solution was concentrated at 80 °C. To synthesize chemical functionalized GQDs, 10 mg bare GQDs dissolved in 10 ml toluene, to this solution 1.44 g of 10 mmol 6-aminoquinoline, 1.23 g of 10 mmol 4- methoxyaniline or 1.39 g of 10 mmol 4- (methylthio) aniline was added and heated at 120 °C for 12 h under vigorous stirring. Then the solid was dissolved in 5 ml toluene and dialyzed using dialysis tubes to remove excess toluene, the dialyzed solution was again concentrated in a rotary evaporator and placed in a vacuum oven at 80 °C until used. Thus, chemically functionalized GQDs showed various emission spectra specifically excitation wavelength at 550 nm and emission wavelength at 605 nm showing red photoluminescence. Furthermore, these functionalized GQDs were used as lumophores to demonstrate light-emitting diodes (LEDs) that have high color purity with green, orange, and red electroluminescence [91].

3.5. One-pot method

The one-pot method is a simple and eco-friendly method to prepare GQDs by reducing the formed GO sheets [92]. It is a chemical reaction that uses organic precursors for the simultaneous formation of graphene quantum dots and to form the porous architecture of GQDs by spontaneous self-assembly [93]. Chun Ke et al. demonstrated a one-pot method for the synthesis of heteroatom-doped graphene oxide/graphene quantum dots (GO/GQDs) mixed by the reaction of hydrogen peroxide to induce decomposition of

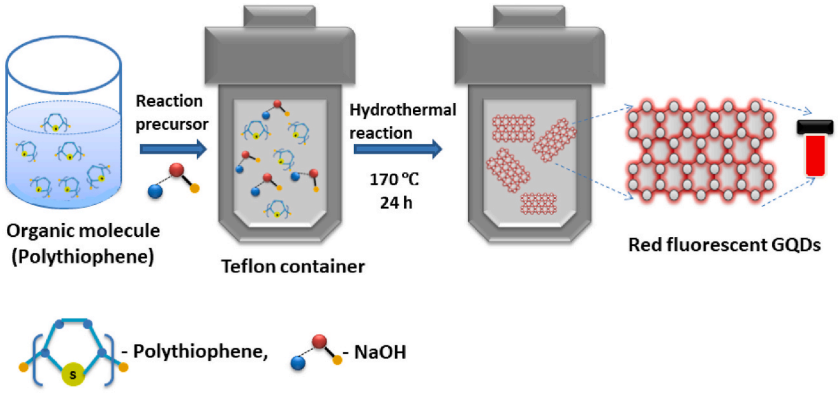

Fig. 9. RF-GQDs preparation by hydrothermal method by using organic molecules as precursors.

Table 1
Comprehensive comparison and comparative analysis of RF-GQDs synthesis methods.

Method	Efficiency	Cost	Environmental Impact	Industrial Feasibility	References
Electrochemical Exfoliation	High (uniform sized, high yield)	Moderate to Low (graphite electrodes, simple electrolytes, mild solvents)	Moderate (low risk, less-hazardous reagents, proper and potential recycling of dissolved salts)	High (scalable, less complex, simple setup)	[66–68]
Solvothermal	High (high-quality and luminescent GQDs)	Moderate (expensive organic solvents, high energy consumption)	High (hazardous waste, potential handling risk)	Moderate to low (less feasibility, high cost, uneconomical)	[75]
Pyrolysis	High (good yield, high quality, simple)	Low (inexpensive carbon precursors)	Low (environmentally friendly, less to non-hazardous chemicals)	High (cost-efficient, highly scalable)	[82,83]
Hummer's Method	Moderate (moderate consistency, complex, reasonable yield)	Moderate (strong oxidizers)	High (hazardous chemical waste)	Low to Moderate (average scalability, safety and regulatory issues)	[90,91]
One-Pot Method	Moderate (simple with moderate yield)	Low (less expensive-common reagents)	Low to Moderate (mild-reaction conditions, minimal waste, eco-friendly reagents)	High (highly scalable, simple and single-step reaction setup)	[96]
Microwave-Assisted Hydrothermal	Moderate (uniform particle size, fast)	Moderate (microwave reactor, accessible precursors)	Low (minimal wastage, non-toxic)	High (rapid, minimal operational cost)	[102]
Hydrothermal	High (uniform sized, high yield)	Low to Moderate (general solvents)	Low (balanced processing conditions, nontoxic reagents)	High (simpler setup, highly scalable)	[109]

graphene oxide by hydroxyl radical produced by NH_4OH and thiourea-mediated dissociation of hydrogen peroxide in alkaline condition, the procedure presented in Fig. 7 [94,95].

Graphite powder was used to prepare GO using the Hummers' method. Red emitting GQDs/GO (R-GQDs/GO) were prepared by incubating 5 ml of 0.5 mg/mL of synthesized GO allowed to react with 4 ml of 30 % H_2O_2 and 0.228 g of thiourea for 10 min at 80 °C. To obtain R- GQDs/GO the product was centrifuged and the precipitate was then sonicated and 5–10 nm sized R- GQDs/GO was attained. The as-synthesized R- GQDs/GO had optical property [96].

3.6. Microwave-assisted hydrothermal method

This method is the combination of hydrothermal and microwave-assisted techniques enabling fast and productive methods, shortening the time duration of GQDs synthesis called microwave-assisted hydrothermal method (MAH) [23]. Microwave-assisted synthesis involves the use of microwave radiations as a heat source to reduce the time in synthesizing GQDs [97]. By combining hydrothermal and microwave methods, aiming to achieve high pressure and high temperature in a short time reduced from several minutes to several hours in a closed reaction system [98]. Tang et al. reported microwave-assisted hydrothermal method (MAH) for the synthesis of a layered structure of nitrogen-doped graphene quantum dots (N-GQDs) having a broad emission spectrum ranging from deep UV, visible, and near-infrared emission, illustrated in Fig. 8 [99–101].

The layered structure of N-GQDs was exclusively responsible for broadband emission containing wide-ranging delocalized π electrons consisting of a large conjugated system. Therefore, glucose and ammonia were used as the source for the preparation of N-GQDs. In the preparation method, 1 g of glucose and 0.5 ml of aqueous ammonia consequently dissolved in 7.5 ml of deionized water (DI), the solution was mixed well and diluted up to 5-fold using DI water. Then 2.5 ml of the solution eluted in a glass bottle and heated in a microwave oven at 280 W for 1, 3, 5, 7, and 9 min for obtaining a series of N-GQDs with different diameters, and the samples were dialyzed against DI water using molecular weight cutoff of 1000. These synthesized N-GQDs exhibited broadband PL emission in the NIR region with an emission peak at ~862 nm and ~917 nm when excited at 808 nm, which could be applied in various fields like broadband photodetectors, bioimaging, solar cells, and fiber communications [102].

3.7. Hydrothermal method

The hydrothermal method is the most commonly used method for synthesizing GQDs, similar to that of the solvothermal method. This system uses water as a solvent and provides a closed atmosphere to form high temperature and pressure influencing the particle size of GQDs to acquire good crystalline morphology [103]. In this approach organic molecules (carbon) or polymers suspended in water form reaction precursor at high temperature to form uniform-sized GQDs [104]. Graphitic structure is also established by using solvents (ethanol) to generate hydroxyl radical, that can split the cellulose chains in the precursors used and aids in the formation of nanosized GQDs [105]. Ge et al. synthesized GQDs using polythiophene (PT2), 30 mg of PT2 was dissolved in 40 ml of 0.5 mM NaOH solution represented in Fig. 9 [106–108].

The mixture ultrasonicated for 30 min and transferred to autoclave and heated at 170 °C for 24 h, the formed GQDs were filtered using a 0.22 μm membrane removing larger particles and residual NaOH, GQDs were dialyzed against distilled water. The synthesized GQDs showed broad absorption of strong deep-red emission and were further used as PDT agents in photodynamic therapy [109].

Table 2
The parameters for synthesized RF-GQDs based on its spectroscopic technique.

Main-methods	Subclassification	Diameter (ca.) (nm)	Raman peaks/ bands (cm^{-1})		UV–vis absorption peaks (nm)		PL emission peaks (nm)	Quantum yield % (QY)	Functional group/element responsible for red luminescence	Applications	References
			D peak	G peak	(π- π*)	(n- π*)					
Top-down	Electrochemical exfoliation	3	1350	1601	227	–	610	1.8	$SO_4^{\bullet -}$ radical responsible for red fluorescence ($SO_4^{\bullet -}$ acts as scissors to cut graphene into sp^2 clusters)	In vitro Cellular imaging - HeLa cells (cytoplasm and cell membrane labelling)	[66]
	Electrochemical exfoliation	5.5	–	–	230 268 360	–	613	15.5 s	DBM (dibenzoylmethane) and Phen (1, 10-phenanthroline) chelating ligands generates red luminescence as its conjugated to GQDs first then to Eu (III) to generate luminescence	In vitro Bio-imaging- MCF7 cell (cytoplasm and cell membrane labelling) and In vivo and Ex vivo tumor imaging- as Bio-probe in HeLa tumor-bearing nude mice	[67]
	Electrochemical exfoliation	10.6	~1350	~1580	292–316	520–560	625	9.1	Under notably increasing pH from 11 to 14, red fluorescence was obtained where lactone structure was converted to quinone	In vitro Cellular imaging- HeLa cells (temperature and pH response controlling probe)	[68]
	Solvothermal	4.52	1348	1570	–	338 (C=O) and (C–N) 467 (C=N) and (C=S) 557 (C=S)	640	8	Heteroatoms S and N from thiourea (used as N and S source) possibly be the reason for red emission	In vitro Bio-imaging- A549 cells and Photocatalyst application	[75]
	Microwave-assisted hydrothermal method	3 and 5.8	–	1599	–	268 (C=N) 310.5 (C=O)	~862 (NIR) ~917 (NIR)	6.8 and 11.3	Ammonia (carbon source) aids in doping of nitrogen (N) on GQDs resulting in red emission as size increases	Application in the fields including Bio-imaging, photodetectors, fiber communications and solar cell.	[102]
	Hummer's method	15.96	1340	1581	401	456	648	21.52	Nitrogen group got integrated into GQDs via Aniline group resulting in formation of red emission	Application in Bio-sensing	[90]
	Hummer's method	~3	–	–	305	470≤λ ≤ 590	605	20.9	Oxygen and nitrogen chemical groups (form amine group) associated to aniline derivatives (4-(methylthio) aniline, 6-aminoquinoline, 4-methoxyaniline) produced red emission	LED demonstration with high color purity	[91]

(*continued on next page*)

Table 2 (*continued*)

Main-methods	Subclassification	Diameter (ca.) (nm)	Raman peaks/ bands (cm^{-1})		UV–vis absorption peaks (nm)		PL emission peaks (nm)	Quantum yield % (QY)	Functional group/element responsible for red luminescence	Applications	References
			D peak	G peak	(π- π*)	(n- π*)					
Bottom-up	Pyrolysis	4.66	1355	1580	238	335	580	54.5	Strong fluorescence has resulted from the amino group of L-glutamic acid (natural amino acid) that coated the surface of GQDs with nitrogen	In vitro fluorescence imaging- MH-S cells (murine alveolar macrophage cells) labelling both cytoplasm and cell membrane, In vivo imaging- BALB/c-nu mice and detecting H_2O_2 using catalytic activity of GQDs.	[82]
	Pyrolysis	2.37	–	–	–	–	622	1.7	COOH and amine group, COOH reacts with amine group to form -CONHR, amidation causes red shift.	In vitro Bio-imaging- Human primary glioblastoma cell line 87 (U-87).	[83]
	Hydrothermal	2–6	1347	–	400–700 nm (broad absorption)		680	~1.3	Polyethylene glycol derivatives (carbon source) displayed red emission with more oxygen group absorbed onto GQDs	Photodynamic therapy (PDT) and In vitro cell imaging- HeLa cells (cellular imaging- labelling cell cytoplasm only and PDT- cell death) and In vivo fluorescence imaging and PDT- female BALB/nu mice with breast cancer (tumor growth suppression in PDT)	[109]
	One-pot method	5–10	1360	1600	250	300	1 %	1	Thiourea effectively disintegrates hydrogen peroxide (H_2O_2) to hydroxyl radicals, favored in emitting red emission	As a future scope R-GQD/GO could be applied as fluorescent probe and in bioimaging	[96]

3.8. Comparative analysis of RF-GQDs synthesis methods

Red fluorescent graphene quantum dots (RF-GQDs) are synthesized using several techniques, each having unique benefits and drawbacks concerning industrial scalability, cost, efficiency, and environmental impact, Table 1 summarizes the potential for scaling up the production of RF-GQDs. Three processes stand out for their high yield and efficiency: pyrolysis, hydrothermal, and electrochemical exfoliation. Electrochemical exfoliation offers uniform-sized GQDs and a simple, scalable setup [66]. Pyrolysis is a very viable process for industrial applications as it is highly economical, uses straightforward organic precursors, and generates minimal environmental waste [82]. The hydrothermal method also excels in efficiency, affordability, and environmental friendliness, utilizing water-based processes to produce uniform-sized GQDs under mild conditions [109].

On the other hand, Hummer's approach, while successful in generating GQDs, necessitates hazardous chemicals and complex multi-step processes, which escalates costs and negatively affects the environment, making it less feasible for industrial use [65]. Despite the efficiency, cost of solvothermal methods is moderate, they require high-pressure vessels, which may restrict their scalability. Additionally, the solvents utilized in these methods are highly volatile and toxic, which could pose concerns to human health and the environment if not carefully managed [75]. The one-pot method is simple, inexpensive, and ecologically benign, making it ideal for large-scale production, even though its yields could be modest [96]. Hydrothermal synthesis aided by microwaves offers excellent scalability and efficiency besides fast synthesis; yet, the expense of the equipment required for this process can increase [102]. In general, pyrolysis, hydrothermal, and electrochemical exfoliation are the techniques of choice for commercial applications because they combine high efficiency, reduced environmental effect, and scalability, eventually providing a feasible route for the large-scale synthesis of RF-GQDs.

4. Characterization methods

In general, to characterize GQDs based on their properties various characterization techniques have been used. The size, morphology, and crystalline structure of GQDs characterized by Transmission electron microscopy (TEM) [110,111], optical properties studied using UV–vis absorption and photoluminescence excitation spectra (PLE) [112,113], structural components i.e., chemical bond and functional groups on the surface of GQDs analyzed using Fourier transform infrared spectroscopy (FTIR) and X-ray photoelectron spectroscopy (XPS) [114,115] and structural defects investigated by Raman spectroscopy for synthesized RF-GQDs [116]. Table 2 depicts the potential characteristics and parameters for synthesized RF-GQDs based on spectroscopic techniques.

4.1. Comparing the synthesized RF-GQDs based on their spectroscopic techniques

Several key aspects can be highlighted to determine the best synthesis method on basis of spectroscopic techniques. The pyrolysis process with L-glutamic acid (natural amino acid) as a carbon source appears to be the best strategy. This approach has the maximum quantum yield of 54.5 %, revealing outstanding fluorescence efficiency, and produces strong emission at 580 nm, which is crucial for red luminescence applications [82]. Electrochemical exfoliation methods yield GQDs with uniform sizes, particularly those with diameters between 3 and 5.5 nm [66,67]. TEM analyses show that the solvothermal [75] and Hummer's techniques [90] generate GQDs with good graphitic lattice and crystallinity, as evidenced by strong D and G Raman peaks. In terms of thickness, GQDs from electrochemical exfoliation and the solvothermal technique tend to be a few atomic layers thick. Pyrolysis [82] and hydrothermal techniques [83] outperform aqueous dispersion due to functional groups comprising COOH, amine, and polyethylene glycol derivatives. The hydrothermal [109] approach also exhibits effective electronic transitions, including a broad absorption range of 400–700 nm and a strong emission at 680 nm, which is useful for photodynamic therapy and fluorescence imaging. Overall, the L-glutamic acid-based pyrolysis approach appears to be the most promising, with high fluorescence efficiency, sustained red emission, excellent water

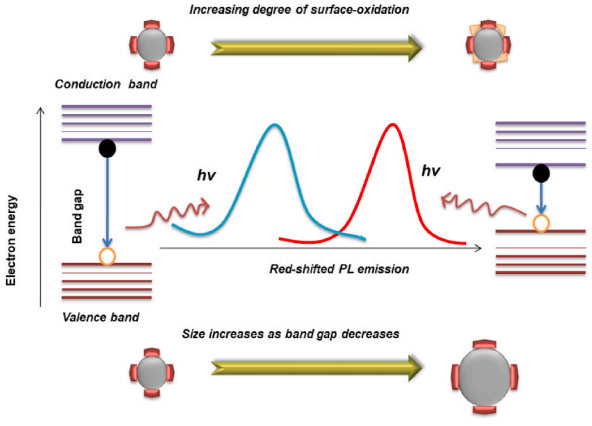

Fig. 10. Photoluminescence mechanism of quantum confinement in Graphene quantum dots described by size and surface-oxidation. Increasing size and surface-oxidation; decreases the band gap, thus exhibiting red shift.

dispersion, and appropriate electronic transitions for a wide range of bio-imaging and sensing applications.

5. Photoluminescence (PL) tunability

Up to now, PL tunability of GQDs is always the most important characteristic because multicolor emitting GQDs can be tuned from blue to red by adjusting their size-dependent quantum confinement, surface chemical modification, edge effects, and chemical doping [117]. In PL mechanism quantum confinement in GQDs creates a bandgap which plays a significant role in emission spectra and the

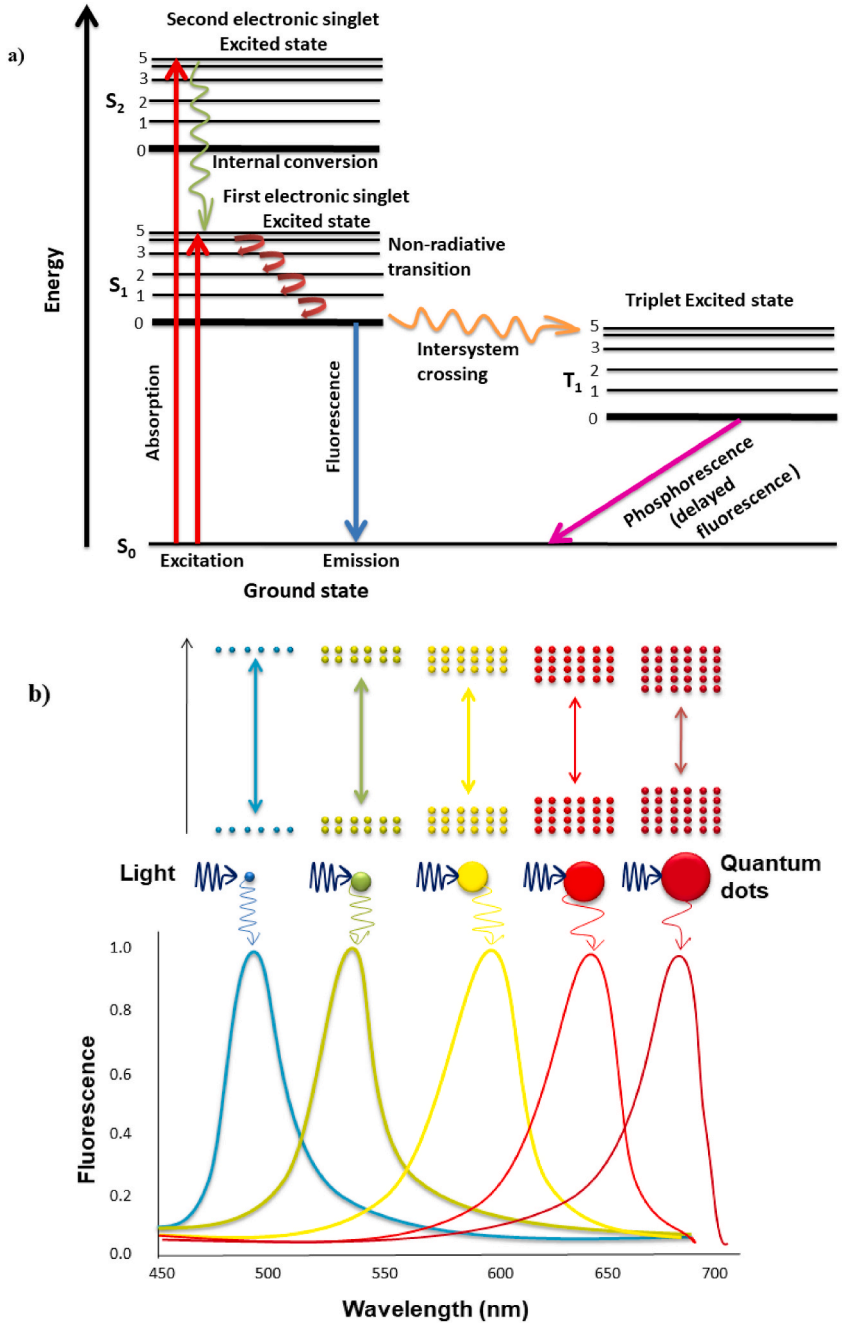

Fig. 11. a) Picture portrays jablonski diagram illustrating the fluorescence mechanism describing absorption and emission. The absorbed photon is excited to higher energy level and return to its ground state as fluorescence, again the excited electron undergoes intersystem crossing to excited triplet state and decays back to the ground state as phosphorescence. b) The schematic representation of a change in color emission based on bandgap and size variation.

modification in bandgap also known as energy gap provides the redshift [118]. A decrease in bandgap corresponds with an increase in the size of GQDs showing red shift [17]. Surface defects on GQDs arise from the oxidation of surface groups resulting in red-shifted PL spectra. The PL tunability and bandgap can be controlled by changing the size, shape, and increasing excitation wavelength of prepared GQDs, as shown in Fig. 10 [119,120]. PL emission usually attributes to electronic transitions between the lowest unoccupied molecular orbital (LUMO) to the highest occupied molecular orbital (HOMO) respectively [121,122]. Jin et al. reported red-shifted PL emission upon the chemical functionalization of GQDs with an amine group resulted from pH change due to protonated or deprotonated functional groups. This study was the first to identify that charge transfer between GQDs and amine functional groups were responsible for tuning and change of bandgap in GQDs. GQDs and amine group functionalized GQDs were prepared by Hummers' method by adding polyethylene glycol (PEG-diamine) to form alkyl amine-functionalized GQDs (GQDs-NHR). The PL shift of GQDs-NHR was greater than unfunctionalized GQDs showed maximum PL position at 528 nm which was red-shifted; this clearly states that redshift behavior was initiated from functionalization. The GQDs-NHR obtained opposite pH-dependent PL spectra as compared with GQDs confirming the PL shift was from functionalization or quantum size effects [123]. Yuan et al. reported a high size-dependent redshift on absorption with photoluminescence (PL) and two-photo photoluminescence (TPPL). They synthesized GQDs-ht1 (hydrothermal) from $C_{96}H_{30}$ showed higher charge transfer efficiency and redshift of both absorption and fluorescence emission. GQDs-ht1 obtained absorption peak at 230 nm and one-photon PL peaks at 624 nm when excited at 400 nm and by inducing one and two-photon absorption it showed 20 nm of redshift between PL spectra when excited using 800 nm infrared femtosecond laser light [124]. Ain et al. tailored chemical doping of GQDs with chlorine, nitrogen, boron, sodium, and potassium as a dopant to exhibit a change in PL tunability, Cl- and N-doped GQDs revealed red-shifted PL. By narrowing the bandgap red-shifted PL spectra was obtained which might be of a decrease in their bandgap. Cl-doped GQDs showed a redshift due to an increase in the concentration of oxygen-containing groups reducing the band gap [117].

Yuan et al. fabricated a red-shifted PL peak positioned from 522 to 575 nm when the pH values increased from 1 to 11 which was mostly due to the deprotonation of oxygenic functional groups, the as-synthesized MCF GQDs maximum absorption peak from 292 to 316 nm indicating a redshift, this redshift fluorescence was used in cell culture to view different pH solutions [68]. Liu et al. reported a red-shifted absorption peak of $(GQD/DBM)_3EuPhen/GQD$ with a sharp emission band at 613 nm matching to emit red fluorescence by deactivating excited states $^5D_0 -> ^7F_2$of Eu (III), these red PL has application in bio-labeling [67]. Qu et al. reported the synthesis of S, N co-doped GQDs gave red PL emission at 640 nm when excited at 480 nm [75]. Gao et al. reported a redshift in PEI_{600}GQDs by explaining its PL emission as the particle size increases, luminescence energy got moved towards lower energy where, narrowing of the bandgap leads to red shift [83]. Chhabra et al. synthesized R-GQDs exhibiting red-shifted emission peak at 558 and 648 nm when excited at 410 nm [90]. Chun Ke et al. reported heteroatom-doped graphene quantum dots showing red-shifted absorption peak at 630 nm when excited at 420 nm indicating larger GQDs attains redshift in emission [96]. Tang et al. reported the PL emission of synthesized N-GQDs with emission peak centered at 915 nm with increasing size equals to 5.8 nm when excited with a wavelength of 808 nm [102].

5.1. *Mechanism enabling red emission in graphene quantum dots*

Red emission in graphene quantum dots (GQDs) is enabled by many specialized methods that include the control of electronic states and band gaps. The inclusion of various surface functional groups facilitates red emission by generating localized electronic states within the bandgap. Oxygen-containing compounds like carboxyl (-COOH) and carbonyl (C=O) generate mid-gap states, whilst hydroxyl (-OH) groups affect surface states, each of which helps minimize energy emissions [125,126]. Nitrogen doping introduces amino (-NH2) and amide (-CONH2) groups, which stabilize and add new energy levels to the bandgap, resulting in increased red emission. Sulfur-containing groups such as thiol (-SH) and sulfonate (-SO3H) generate defect states and extra electronic states, shifting the emission towards the red region [83,127].

Other groups, such as epoxy (-O-) and phenyl (C6H5), alter electrical characteristics and promote conjugation, resulting in red-shifted emission. These functional groups work together to alter the electronic structure of GQDs, resulting in red photoluminescence. The fundamental mechanism underlying the red emission is that molecular fluorophores adhere to the surface of the GQD core and dominate the fluorescence. Larger GQDs have significant surface oxidation, which introduces oxygen-rich groups like carbonyl and carboxyl, resulting in localized mid-gap states that allow these molecular fluorophores to transition at lower energy levels. Larger sp^2 domains in GQDs increase π-π* interactions and π-electron delocalization, reducing bandgap energy and resulting in red emission [128,129].

Red-emitting GQDs have the smallest transition band gap energy due to their extensive surface functionalization and large size, leading to a lower energy difference between the valence and conduction bands [91,130]. Furthermore, environmental influences such as acidic pH levels can protonate surface groups, affecting electrical states to favor red emission. Aggregation-induced emission (AIE) effects, in which GQD aggregation reduces intramolecular motions while increasing intermolecular interactions, also result in red-shifted emission. These mechanisms, backed up by subsequent studies, highlight the importance of surface functionalization, doping, quantum size effects, and environmental factors in generating red emission in GQDs [83,127].

6. Fluorescence mechanism

The mechanism of fluorescence is the property of an electron when excited with light at a particular wavelength, depends on the absorption the electrons get excited from its ground state to its excited state. The electrons in higher energy level will remain for short time and relaxes back to its ground state by emitting some energy known as fluorescence, the emitted light usually has a longer

wavelength and lower energy as compared to the absorbed light, the mechanism depicted in Fig. 11a [131–133]. Fluorescence mechanism in GQDs helps to modulate the color emission, where the bandgap of conjugated π-domains is responsible for fluorescence states, by adjusting the size of conjugated π-domains the color emission can be controlled and adjusted [134] shown in Fig. 11b [135–138]. The fluorescence mechanism is also facilitated by rich surface defect states which regulate the fluorescence emission in GQDs [132]. In GQDs the fluorescence color can be tuned by simply varying the excitation wavelength with the property of excitation-dependent or independent photoluminescence (PL) [139].

6.1. Excitation dependent emission

Excitation-dependent photoluminescence (PL) has a tunable fluorescence emission, where the intensity of emission decreases in a long-wavelength window. Excitation dependent emission significantly matches size-dependent PL showing red fluorescence by an increase in size [139]. Lai et al. explained the multicolor fluorescent mechanism that gave excitation-dependent multicolor PL. They reported, to obtain a PL emission only excitation wavelength could be tuned without tuning the structure of GQDs having excitation-dependent PL emission. As the excitation wavelength increases higher redshift occurs, multicolor emission was accomplished when excited from 260 to 520 nm showing emission wavelength at about 450–540 nm to study possible excitation-dependent PL spectra [14]. Tang et al. reported the synthesis of N-GQDs exhibited broad PL peak with excitation wavelength-dependent PL when excited with Xe lamp as an excitation source. In a larger conjugated π electron system, a longer excitation wavelength was required to satisfy the absorption to obtain an excitation wavelength-dependent emission. Size-dependent PL emission is also observed for N-GQDs, with a diameter of 1.7 nm the emission peak was centered at 450 nm and obtained a redshift as the size increased. With the size of 5.8 nm, the peak obtained at 582 nm when excited at 808 nm [102]. Chhabra et al. fabricated the synthesis of GQDs with carboxylic acid groups on their surface, showed excitation-dependent PL behavior with a redshift where the peaks shifted at different excitation wavelengths by varying the size and quantum confinement, lower wavelength energy transitions p*-p were used for excitation of sample to attain excitation-dependent emission [90]. Gao et al. reported PEI_{600} GQDs showed excitation-dependent emission property, emission maximum shifted from 590 to 690 nm when excitation wavelength changed from 500 to 650 nm. PEI_{600} GQDs had exhibited different PL properties that include different sizes and emissive sites [83]. Wu et al. fabricated highly fluorescent graphene quantum dots with strong excitation-dependent emission of 800–850 nm near-infrared (NIR) fluorescence also good photoluminescence shifted from blue to a red range by excitation-dependent mechanism [82]. Cushing et al. gave the phenomenon of excitation dependent wavelength depends on the fluorescence peak in a polar solvent helped to originate the giant red-edge effect. The OH and COOH groups on the surface of GO sheets loosen the mechanism by confirming that these functional groups were responsible for strong excitation wavelength-dependent fluorescence. Further mentioned the fluorescence timescale emission could strongly affect excitation wavelength-dependent fluorescence behavior, which gives a giant red-edge effect making the fluorescence peak dependent on excitation wavelength [140].

6.2. Giant red-edge effect

The giant red-edge effect (REE) in graphene oxide (GO) is an intense shift in fluorescence emission spectra with different excitation wavelengths that is much more pronounced than in traditional fluorophores. The REE, which occurs when the emission spectra shift to longer wavelengths as the excitation wavelength increases, is generally small in most fluorophores [141,142]. However, in GO, this effect is extremely prominent, hence the epithet "giant." This effect is caused by the heterogeneous structure of GO, which consists of sp2-hybridized carbon domains interspersed with sp3-hybridized carbon-oxygen groups, resulting in a wide range of electronic states, including π-π* and n-π* transitions. Shorter wavelengths excite higher-energy levels, resulting in blue-shifted fluorescence, whereas longer wavelengths excite lower-energy states, resulting in red-shifted fluorescence. Furthermore, mechanical strain can modify the local electronic environment by compressing or stretching the carbon lattice, which can adjust the energy levels and improve the REE. Research illustrates that in the absence of strain, emission peaks greatly shift; for instance, from 460 nm to 600 nm when excitation

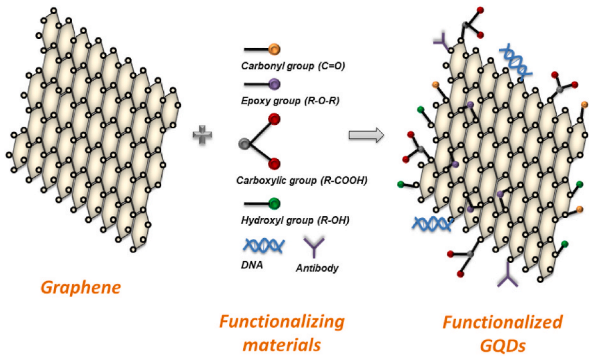

Fig. 12. Represents the edge functionalized GQDs. The surface is functionalized with various functional groups, doping of chemical molecules, and biomolecules; such factors productively enable GQDs to alter its structure.

wavelengths vary from 400 nm to 520 nm; strain then amplifies this shift. The giant REE in GO arises from its unique heterogeneous composition results in the remarkable degree of control over GO's fluorescence through mechanical deformation and excitation wavelength underscores its promising uses in flexible electronics, sensors, and optoelectronic devices [143].

6.3. Excitation-independent emission

Despite the size distribution of GQDs, the excitation-independent emission additionally hinges on the surface passivation states [144]. Excitation-independent emission solely depends on surface functional groups like oxygen and nitrogen that provides different vibration relaxation for excitation-independent emission [145]. Joffrion et al. reported the synthesis of excitation independent GQDs by microplasma assisted electrochemical process attaining red emission. This technique facilitates strict excitation-independent photoluminescence, where a single excitation wavelength of 405 nm was used for different emission from 506 to 653 nm indicating emission wavelengths remained the same even when excitation wavelengths were changed. Excitation-independence was accomplished by high-level surface passivation by oxygen; and a higher concentration of glucose and long process time showed longer emission wavelengths helped to attain excitation-independent behavior which was used in multi-target bioimaging, display technology, encryption, and lasing applications [146]. Chun Ke et al. reported the synthesis of GQDs exhibited excitation-independent emission of four different fluorescence peaks included red emission when excited at different wavelengths associated to prove excitation-independent emission. Size-dependent emission was also observed in respective to time-resolved fluorescence decay, the fluorescence was found to shorten with an increase in the size of GQDs from 2 to 3, 2–5, 4–8 to 5–10 nm respectively with average fluorescence from 3.37, 2.75, 1.07 ns [96]. Qu et al. synthesized three-color emissions from S, N co-doped GQDs attained excitation independent-wavelength by PL spectra luminescence at 440, 550 and 650 nm with different excitation wavelength ranges of 340–420 nm, 460–540 nm, and 560–620 nm. Further added each emission was related to a single excitation band, and in heteroatom-doping of GQDs the chromophore group on the surface of S, N-GQDs emits light at specific wavelength under a specific range of excitation helped to attain independent luminescent, where energy transfer for independent luminescence does not occur only under different light excitation wavelength [75].

7. Functionalization of RF-GQDs

In general, ordinary graphene sheets are hydrophobic and less interactive and that's the reason why functionalization is important and functionalized graphene material becomes hydrophilic. Simple conversion of graphite to graphene oxide will initiate the graphene functionalization process. Some different functionalization processes of graphene are commonly covalent and non-covalent like edge functionalization, heteroatom-doping of nitrogen, and sulfur on graphene, basal plane functionalization, functionalized graphene self-assembly, asymmetrical functionalization, and basal plane non-covalent adsorption [136]. Heteroatom-doping of graphene increases its usefulness in energy fields, edge and basal plane functionalization tend to increase graphene reactivity, film-forming ability, and its solubility [147]. Functionalization of GQDs with a range of chemical groups like OH, COOH, NH_2, PEG onto the surface of GQDs could modify their basic edge shape creating a multifunctional structure [148], as represented in Fig. 12 [57,149–153]. Chhabra et al. synthesized carboxyl functionalized GQDs with the use of graphite flakes. In this process H_2O_2 and aniline was used as a solution to form functionalized GQDs, the formed GQDs had different electronic states n-π and π*-π transition with amino edges [90]. Kwon et al. synthesized chemically functionalized GQDs using aniline derivatives included an amine group. They reported, using functionalized aniline derived GQDs light-emitting diodes were produced with natural color and high purity. These GQD-LEDs had color purity with exceptionally large FWHM (full width at half maximum) $>$ 100 nm with various energy gaps and electronic states due to the presence of lasting nitrogen and oxygen chemical groups. Through functionalization, intrinsic photoluminescence converted to extrinsic photoluminescence centers due to extrinsic energy levels of aniline derived chemical structures [91]. Jin et al. reported the bandgap tuning mechanism of GQDs via chemical functionalization of the amine group. Amine functionalized GQDs exhibited redshift and the PL shift happened because of charge transfer between the amine functional groups and GQDs, also added change in pH could influence the PL shift owing to electron-withdrawing and electron-donation of functional groups. They also included that this was the first study to tune PL in responsible with charge transfer between functional groups and GQDs. They used diamine terminated polyethylene glycol (PEG-diamine) to oxidize GO, alkyl amine groups were then attached to oxidized GO by the action of epoxy groups, forming alkyl amine-functionalized GQDs (GQDs-NHR). This functionalization does not affect the structure of GQDs but effectively showed a red-shifted PL [123]. Liu et al. prepared GQDs functionalized with noncovalently connecting chelating ligands DBM and Phen with GQDs and Eu (III) to achieve a red fluorescence. These chelating ligands were noncovalently connected to GQDs to produce a stable and water-soluble complex of $(GQD/DBM)_3EuPhen/GQD$ without affecting the size of GQDs after functionalization producing a red emission [67].

7.1. Surface functionalization and biocompatibility

Surface functionalization of RF-GQDs improves their biocompatibility, by integrating functional groups like hydroxyl (OH), carboxyl (COOH), and amine (NH2) to the surface of RF-GQDs, their hydrophilicity increases dramatically, reducing cytotoxicity and promoting improved dispersion in biological environments. This alteration allows RF-GQDs to interact with biological molecules more effectively, increasing their stability and decreasing any possible cell toxicity. For instance, carboxyl functionalization can improve biocompatibility by lowering aggregation and minimizing non-specific interactions with cells. Hydroxyl functionalization reduces their toxicity while increasing cellular absorption, whereas amine functionalization improves their biocompatibility by lowering

toxicity, reducing immunological response, and enabling better integration into biological systems [154,155]. Similarly, adding polyethylene glycol (PEG) can improve biocompatibility by inhibiting protein adsorption and reducing non-specific cellular interactions, hence reducing cytotoxic effects and increasing in vivo circulation time [156].

7.2. Surface functionalization and cellular interactions

Surface functionalization has a significant impact on RF-GQD's cellular interactions. The surface of RF-GQDs contains functional groups such as COOH, NH2, and PEG, which permit both specific and non-specific interactions with cellular membranes and intracellular components. Different functional groups can change the dynamics of cellular uptake: some may increase the rate at which cells internalize GQDs, while others may decrease it. Furthermore, these functional groups can direct GQD localization to specific cellular compartments or organelles, allowing for more precise targeting. Meanwhile, surface functionalization can influence cellular signaling and responses, with a few eliciting particular cellular responses or impacting specific cellular pathways [155,157].

8. Photoluminescence quantum yield

The quantum yield is a measure of photon emission defined by the ratio of the number of photons emitted to the number of photons absorbed [158]. To date there are no definite directions for quantum yield, still, the vibrations of functional groups on the surface edges of graphene quantum dots could enhance the quantum yield [159]. Some important factors for quantum yield can be surface defects, controlling size, surface modification with functional groups and passivation, and doping [160]. Nitrogen or sulfur-doped GQDs can attain an increase in photoluminescence quantum yield (QY) by tuning its PL performance [161]. The presence of functional groups on the surface of GQDs and higher crystallinity of GQDs helps to attain higher quantum yield [162]. As shown in Table 2, the percentage of quantum yield obtained is completely determined by the synthetic route of GQDs. Chhabra et al. reported the synthesis of luminescent GQDs by easy and simple Hummer's method to reveal 50–70 % of quantum yield with different color emitting GQDs, R-GQDs obtained 21.52 % quantum yield by improving GQD preparation condition [90]. As mentioned earlier Liu et al. reported the synthesis of GQDs-europium complex with red fluorescence by an effective, easy to control method electrochemical exfoliation of the graphite rod. The interesting property of Europium trivalent ion Eu (III) complexes exhibited high quantum efficiency of about 15.5 % quantum yield [67]. Chun Ke et al. reported the use of a one-pot method for preparing heteroatom doped GQDs/GO when mixed with thiourea and H_2O_2 to generate red emission. They used a low-cost, simple, and fast method to synthesize R-GQDs/GO which showed a moderate quantum yield of 1 % and they also included that size-dependent quantum yield depends on the quantity of surface defects [96]. Wu et al. fabricated the synthesis of highly fluorescent GQDs using the pyrolysis method which uses a precursor. In this process, the residual L-glutamic acid acted as a surface passivating agent providing high quantum yield. For detection of quantum yield, they used Fluorescein as a reference dye in 0.1 M NaOH, and calculated quantum yield using the following equation, Eq. (1):

$$\phi_X = \phi_{ST}\left(\frac{A_{ST}}{A_X}\right)\left(\frac{I_X}{I_{ST}}\right)\left(\frac{n_{X^2}}{n_{ST^2}}\right) \tag{1}$$

where, X represents a sample and ST-standard, ϕ-quantum yield, I denote measured integrated fluorescence intensity and n-refractive index of solvent. The quantum yield was measured to be 54.5 % in the blue to red range [82]. Qu et al. reported the synthesis of S, N co-doped GQDs using a simplistic solvothermal method, and obtained PL quantum yield of 8 % with red emission [75]. Tang et al. reported the synthesis of N-GQDs using a microwave-assisted hydrothermal method (MAH) using glucose and ammonia. As synthesized N-GQDs showed PL quantum yield between 6.8 % and 11.3 % recorded using FLS920P Edinburgh apparatus [102]. Yuan et al. prepared multicolor fluorescent small-sized GQDs using the electrochemical method. To determine the quantum yield (QY) they used Rhodamine 6G as a reference and calculated using the formula, Eq. (2):

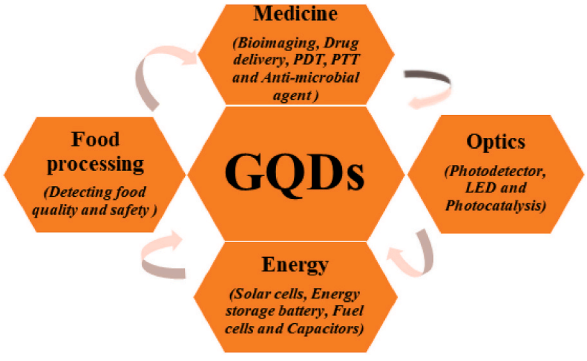

Fig. 13. An overview of GQDs in various other applications.

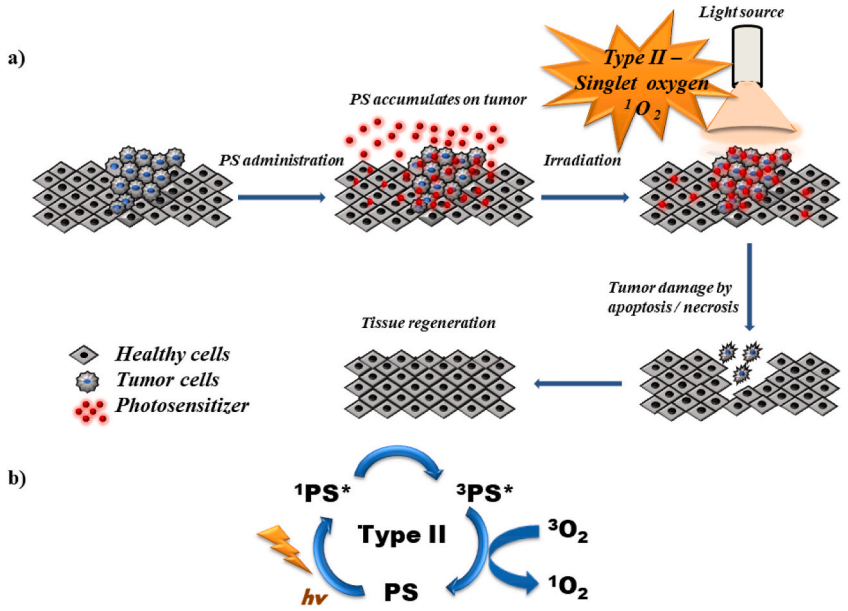

Fig. 14. a) Schematic representation of Photodynamic therapy to kill cancer cells and, b) the action of light, oxygen, and a photosensitizer to produce singlet oxygen.

$$\phi_X = \phi_{ST}\left(\frac{m_X}{m_{ST}}\right)\left(\frac{n_X^2}{n_{ST}^2}\right) \tag{2}$$

where, ϕ-quantum yield, m-slope of the curves, n-refractive index, the determined QY of MCF GQDs was found to be 9.1 % in neutral condition [68]. Tan et al. calculated the quantum yield of synthesized RF-GQDs using Rhodamine B as reference showing 1.8 % quantum yield [66]. Gao et al. measured the quantum yield of as-synthesized red-emitting PEI_{600} GQDs with Rhodamine B (RhB) as reference using the following equation, Eq. (3):

$$Q = Q_R \frac{I}{I_R}\frac{A_R}{A}\frac{n^2}{n_R^2} \tag{3}$$

where, Q-quantum yield, R-reference, I-integrated emission intensity, A-photoluminescent excitation wavelength of UV–vis absorbance, and n-refractive index. The quantum yield of PEI_{600} GQDs was calculated to be1.7 % with 495 nm absorbance wavelength [83].

9. Application

The extensive applications of graphene quantum dots (GQDs) are owing to their good biocompatibility, hydrophilic nature, small-sized, broad absorption spectrum, good water solubility, pH- stability, high singlet oxygen generation, excellent luminescent properties, and possessing good bio-imaging property [163]. Graphene quantum dots due to its unique features achieved a rapid increase in various fields [164]. Comparing GQDs with emission range of UV–visible light, the spectral range of 650–1800 nm is linked to a biological transparency window covering red to near infrared (NIR) region. Throughout this spectral range, lower levels of auto-fluorescence, absorption of photons and scattering from tissues is observed [165]. Red-emitting GQDs are used in the field of biomedical research because red and NIR light penetrate tissues more deeply. GQDs also exhibit captivating properties that make them useful in devices like photovoltaic, supercapacitors and batteries described in Fig. 13 [166–168]. This review particularly focusses on the application of synthesized red fluorescence graphene quantum dots in different fields.

9.1. Biological application

9.1.1. Photodynamic therapy (PDT)

GQDs have a potential application in the field of PDT as a novel photosensitizer (PSs) mainly because of their high ROS (reactive oxygen species) generation, low cytotoxicity, hydrophilic nature, and sufficient singlet oxygen generation to kill the cancerous cells which has been reported in *in-vitro* and *in-vivo* study models [169]. PDT is emerging to be more effective, turning to be a better therapy which could also be an alternative to traditional cancer therapies. PDT uses three essential components; PSs, light, and oxygen, principle behind PDT is the applied PSs get activated when irradiated with light at a suitable wavelength. The activated PSs can convert molecular oxygen into highly reactive singlet oxygen species killing the cancer cells portrayed in (Fig. 14a–b) [170,171]. Ge et al.

reported the synthesis of GQDs with red fluorescence by hydrothermal method and used GQDs as an efficient PDT agent that produced singlet oxygen. They demonstrated GQDs having good PDT efficacy during *in-vitro* and *in-vivo* experiments. HeLa cells were incubated with 40 μl of GQDs (0.4 μM) and 20 μl of Hoechst 33342 (1.8 μM) and the cells were constantly irradiated with 405 and 637 nm lasers, where morphological changes were observed which includes cell shrinkage and numerous blebs formation using laser-scanning confocal microscopy. Dark toxicity and phototoxicity of GQDs and PpIX QDs were compared with different concentrations (0.036–1.8 μM) and irradiating HeLa cells continuously for 10 min, achieving 20 % cell viability at high concentration, where PpIX showed cell viability more than 35 % upon irradiation. In the dark condition, GQDs had less effect on cell viability specifying low cytotoxicity, good biocompatibility, and more PDT efficiency. As in the *in-vivo* experiment, a subcutaneous breast cancer xenograft female mouse was studied for PDT demonstration. GQDs injection of 4 mg kg^{-1} dosage injected into mice and irradiated with white light 400–800 nm observing the destruction of tumor after 17 days killing the cancer cells revealing GQDs as PDT agent and efficiency in cancer treatment [109].

9.1.2. Bio-imaging

GQDs possessing excellent fluorescent property and less cell toxicity it is extended in the field of bio-imaging. As synthesized red-emitting water-dispersible GQDs 40 μl (0.4 μM) used to stain HeLa cells which were labeled only in cytoplasm showed strong PL emission related to fluorescence imaging by Ge et al. [109]. Tan et al. reported the synthesis of small-sized RF-GQDs not including any chemical modification showed its application of bio-labeling for cellular imaging. HeLa cells were incubated with RF-GQDs showed significant cell viability and RF-GQDs labeled both in the cytoplasm and cell membrane with red emission when excited at 488 nm exhibiting outstanding photostability and low cytotoxicity [66]. Liu et al. reported the synthesis of water-soluble red fluorescent $(GQD/DBM)_3EuPhen/GQD$ complex used to label both cytoplasm and cell membrane of MCF7 cells with red emission under 405 nm wavelength excitation and revealed less cytotoxicity [67]. Qu et al. reported the use of S, N-GQDs as probes for imaging live A549 cells. The S, N-GQDs incubated A549 cells displayed strong PL emission when excited at 405, 488, 555 nm with blue, green, and red colors respectively exposing good bioimaging property and attained 70 % cell viability [75]. Wu et al. developed GQDs as fluorescent biomarkers for examining bioimaging property. In *in-vitro* condition murine alveolar macrophage (MH-S) cells were incubated with GQDs, these GQDs showed green and red color upon 458 nm and 514 nm excitation wavelength respectively possessing fluorescence imaging property and GQDs were labeled in both cell membrane and cytoplasm of MH-S cells. Under the *in-vivo* condition, GQDs were subcutaneously and intramuscularly injected into mice and fluorescence images were obtained, when excited with different wavelengths indicating fluorescence imaging ability of GQDs [82]. Goa et al. reported red-emitting PEI_{600} GQDs when added to human primary glioblastoma cell line 87 (U-87) with a concentration of 50 μg/ml, U-87 cells exhibited bright red PL upon excitation with 405 nm light, could penetrate cells without damaging the cell morphology, resulting in low cytotoxicity and bioimaging of cells [83].

9.1.3. Bio-probes

Concerning its excellent photoluminescence, constant photostability, and good biocompatibility graphene quantum dots are used as biological probes to detect DNA, RNA, or proteins and tumor labeling [171]. Liu et al. demonstrated *in-vivo* and ex-vivo imaging of HeLa tumor-bearing nude mice injected with $(GQD/DBM)_3EuPhen/GQD$ complex indicated strong fluorescence in internal organ tumor tissues exhibiting good tumor labeling property acted as bioprobes [67]. Yuan et al. reported dual-sensing probes to check cells at different pH and temperature of synthesized MCF GQDs on human cervix carcinoma HeLa cells. To check the intracellular pH and temperature of MCF GQDs internalized cells, nigericin and Britton-Robinson buffer solution with different pH was added to cells to ensure its equilibrated intracellular pH-induced fluorescence change and temperature-induced fluorescence signals in HeLa cells when excited at 405 nm [68].

9.1.4. Other applications

Moreover, apart from the above-mentioned applications, GQDs have potential applications in various other fields as well. Qu et al. also reported the use of S, N-GQDs in visible light photocatalytic applications, owing to its broad absorption band in visible spectrum S, N-GQDs are combined with currently used TiO_2 composites as photocatalyst for efficient H_2 production under visible light. S, N-GQDs when loaded to TiO_2 it got fixed to the surface of TiO_2 due to its high stability and catalytic activity the H_2 production was maximum [75]. Wu et al. further reported the use of GQDs to detect hydrogen peroxide (H_2O_2) in biomedical content. They included that peroxidase-like catalytic activity of GQDs helped to detect H_2O_2, in the presence of peroxidase substrate ABTS (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) indicated by the color change of the sample [82]. Tang et al. reported the synthesis of nitrogen-doped graphene quantum dots (N-GQDs) having chemical stability, wide range emission and specific photoresponse property made it a promising candidate for broadband photodetector application. N-GQDs photodetector displayed negative photocurrent when irradiated with light and could able to react to UV and NIR light sources [102]. Kwon et al. demonstrated GQDs based LEDs (light-emitting diodes) fabricated to show green, orange, and red electroluminescence with high color purity and attained utmost current efficiency when aniline derivatives were used to chemically functionalized GQDs to change their energy levels to acquire narrow linewidth PL [91].

9.1.5. Experimental findings of RF-GQDs in biomedicine

A noteworthy work by Perini et al. describes a novel use of carboxylated graphene quantum dots (cGQDs) in combination with phototherapy and chemotherapy to treat glioblastoma. The cGQDs show significant fluorescence, which may be useful for deeper tissue imaging, albeit it is unclear if this falls within the red region. Using near-infrared (NIR) light in PTT, which successfully penetrates biological tissues, the cGQDs absorb NIR and convert it to heat, resulting in localized hyperthermia. This heat enhances

membrane permeability, allowing chemotherapeutic medicines to be absorbed more efficiently. Immune cells may migrate towards cancerous areas in response to PTT caused by GQDs, which could improve the effectiveness of immunotherapy against glioblastoma. Although the results show that 3D glioblastoma models, which more closely mimic in vivo conditions than traditional 2D cultures, can improve treatment efficacy, reduce side effects, and potentially enhance immunotherapy, there are still obstacles to overcome. These include the complexity of 3D models, the need for further validation due to limited in vivo data to confirm the treatment's efficacy, and optimization challenges need to be addressed for successful clinical translation and practical application of this approach in glioblastoma treatment [172].

Reagen et al. have developed Red-Emissive Porphyrin Graphene Quantum Dots (PGQDs). TCPP (meso-tetra(4-carboxyphenyl) porphine) and CBDA-2 (*cis*-cyclobutane-1,2-dicarboxylic acid) are combined to synthesize PGQDs. The work highlights the exciting potential of Porphyrin-Graphene Quantum Dots (PGQDs) for imaging and clinical cell labelling applications because of their near-infrared and red emission characteristics. These PGQDs showed minimal cytotoxicity in HeLa cells (up to 200 μg/mL), displaying their biocompatibility and effectiveness for precise biological cell labelling without compromising cell viability. The PGQDs stimulated photostability further improves their suitability for extended imaging analysis. Despite these benefits, there are still constraints to overcome before PGQDs are used in clinical settings. These include ensuring that the particles behave and remain stable in intricate biological environments, adhering to safety standards, and finding precise therapeutic focusing, particularly on target tissues and imaging modalities. Although the preliminary findings are encouraging and suggest that PGQDs have great photostability and low cytotoxicity for deep tissue imaging, more study is needed to confirm their safety and effectiveness in clinical scenarios and to successfully negotiate the regulatory approval process [130].

Valimukhametova et al. group investigated the potential of Nd-NGQDs (Neodymium-doped), Ho-NGQDs (Holmium-doped), Yb-NGQDs (Ytterbium-doped), NGQDs (Nitrogen-doped), and RGQDs (Reduced) as near-infrared fluorophores for biomedical multiplex imaging applications by investigating their cytotoxicity, internalization/excretion in HEK-293 cells, and optical characteristics. High contrast imaging was made possible by the GQDs' non-toxicity at concentrations up to 0.5–2 mg/ml, according to biocompatibility evaluations performed using the MTT assay. The GQDs exhibit up to 1.34 % quantum yields (QYs) of NIR emission inside the NIR-I and NIR-II biological windows. GQDs displayed their appropriateness for cellular imaging and tracking, as presented by the internalization and excretion patterns, which demonstrated that they maximally accumulated in cells in 6–12 h and were either expelled or destroyed after 24 h.

The study also demonstrated the viability of multiplex imaging by concurrently introducing all five GQD types which emit at various near-infrared wavelengths into cell cultures, allowing for the tracking and differentiation of multiple agents. Although the GQDs demonstrated significant photostability and great biocompatibility, enabling prolonged imaging sessions, their typically low quantum yields may need longer integration times for efficient imaging. The study, which mainly concentrated on in vitro applications, highlighted the need for additional in vivo research to confirm the clinical applicability of GQDs and pointed out potential limitations for deep tissue imaging. Additionally, the imaging depth of the GQDs is limited to a few centimeters, which presents difficulties for deep tissue imaging [173].

9.1.6. Obtaining regulatory approval for clinical applications

Red emission graphene quantum dots (GQDs) require rigorous preclinical and clinical studies to demonstrate their safety, efficacy, biocompatibility, extensive testing to determine the pharmacokinetics, biodistribution, and potential toxicity of GQDs used in photothermal and photodynamic therapies. Biodistribution achieved by targeted delivery of GQDs to tumor sites while minimizing unintended side effects. Surface modifications, like PEGylation, enhances solubility and extend circulation time. Functionalizing GQDs with targeting ligands (antibodies or peptides) enhances their specificity to cancer cells, improving their therapeutic index through enhanced permeability mechanism and retention (EPR) effect.

For rf-GQDs to be safely and effectively removed from the body and prevent long-term toxicity, biodegradation is necessary. Functionalized rf-GQDs that degrade into non-toxic byproducts under physiological conditions can be eliminated through renal routes, lowering the risk of chronic buildup. Beneficial biodegradation profiles with benign end products that the body naturally eliminates have been reported in studies. The Hefei Institutes of Physical Science's metal-free GQDs, demonstrate significant tumor inhibition with few off-target effects, exhibiting the kind of robust preclinical results needed for regulatory approval. Furthermore, to guarantee consistency and reproducibility, adherence to Good Manufacturing Practices (GMP) and comprehensive documentation of the synthesis and functionalization procedures are essential. To address any long-term safety concerns, regulatory bodies like the FDA and EMA also demand comprehensive clinical trial data that show the therapeutic advantages of GQDs over current treatments. In-depth clinical trial results that show the therapeutic advantages of GQDs over current treatments and address any long-term safety concerns are also required by regulatory bodies like the FDA and EMA. The path toward their future usage in medical applications is being paved by developments in the understanding of their characteristics and possible therapeutic advantages. Achieving this goal will call for meticulous scientific investigation and strategic collaborations with regulatory agencies [174–176].

10. Challenges and future perspective

Red fluorescent graphene quantum dots have shown great promise as a nanomaterial for a range of biological uses, such as photodynamic and photothermal cancer treatments. Nanoscale graphene fragments have numerous advantages, making them ideal for medicinal applications. They have attracted a lot of attention lately because of unique structure-related traits that include many aspects like optical, electrical, and optoelectrical properties. Although GQDs have various benefits for treating cancer, some significant drawbacks need to be considered in account.

10.1. Reproducibility

The reproducibility of RF-GQD synthesis is critical because it is influenced by a variety of circumstances, resulting in discrepancies that have a substantial impact on their practical utility. The following are critical factors: i) Variations in precursor materials: inconsistent results might arise from variations in the purity and kind of carbon precursors, such as glucose, citric acid, or graphite, between batches and suppliers. Precursor impurities can introduce undesired functional groups or defects, impacting the final product's characteristics. ii) Variations in reaction parameters, such as temperature, pressure, and reaction time, are important because mere deviations in these parameters can greatly impact the stability, emission wavelength, and quantum yield [66]. iii) The accuracy of experimental setups: slight variations in the electrolyte concentration during electrochemical exfoliation or specific temperatures and pressure in solvothermal and hydrothermal techniques can drastically change the optical characteristics, quality, and size distribution. iv) Post-synthesis treatment: Substantial standardization is required for steps like surface functionalization and purification. Inconsistent post-synthesis procedures, such as dialysis, centrifugation, and chemical functionalization, might cause changes in optical characteristics and biocompatibility. These processes need to be standardized to achieve reliable quality [177–179].

10.2. Impact on practical utility

Fluctuations in the synthesis parameters of red fluorescent graphene quantum dots (RF-GQDs) have a major effect on their practical utility. In bioimaging, variations in emission spectra and fluorescence intensity can lead to unpredictable imaging outcomes, hence compromising the precision and dependability of diagnostic methods. This fluctuation might result in low contrast and bad resolution in imaging, which makes it challenging to follow the distribution of RF-GQDs in vivo or differentiate between various biological structures. The performance of the sensor in practical applications may be impacted by this, as it may result in inaccurate target molecule detection and quantification. RF-GQDs' safety and effectiveness as photosensitizers in photodynamic therapy can be impaired by changes in quantum yield and stability. Elevated fluctuations may lead to an inhomogeneous generation of reactive oxygen species, which could jeopardize the effectiveness of therapeutic interventions and could cause inadvertent damage to adjacent healthy tissues or insufficient treatment of cancer cells. Thus, maintaining RF-GQD synthesis consistency is essential for their efficient and dependable use in these cutting-edge biomedical domains [180,181].

10.3. Recommendations for improving reproducibility

It is important to develop and adhere to standardized synthesis protocols and provide detailed information about experimental conditions like precursor specifications, specific reaction parameters, and post-synthesis treatments. Conducting inter-laboratory reproducibility studies can help promote consistency among different laboratories. Additionally, implementing strict quality control procedures, such as analysing each batch of RF-GQDs for critical attributes (size distribution, photoluminescence yield, emission wavelength), is essential to ensure uniformity and reliability.

10.4. Scalability and economic consequences

The scalability of red fluorescent graphene quantum dot (RF-GQD) synthesis methods can indeed meet the requirements of the industry, particularly through electrochemical exfoliation, pyrolysis, and hydrothermal methods. These technologies provide excellent effectiveness and yields, which are critical for addressing large-scale manufacturing requirements. Pyrolysis is one method that ensures economic viability because it uses inexpensive organic precursors and generates minimal environmental waste [82]. Electrochemical exfoliation corresponds perfectly with industrial scaling requirements due to its simple setup and reliable product quality [66]. The hydrothermal method is appropriate for continuous, large-scale operations because it uses aqueous processes, which lower costs and their impact on the environment. The hydrothermal approach is suitable for large-scale operations as it involves aqueous processes that reduce costs and environmental effects [109].

Hummers' method and solvothermal methods, on the other hand, are more expensive and environmentally hazardous since they involve complicated procedures and harmful chemicals. However, they can be made more economically and scalable by utilizing advancements in green chemistry [91]. Although effective and scalable, the microwave-assisted hydrothermal process demands specialized equipment, which may increase early investment expenses, however, it offers quick production with negligible environmental impact [102]. Thus, selecting scalable, economical techniques with reduced environmental impact such as hydrothermal, electrochemical exfoliation, and pyrolysis aligns with economic effectiveness and industrial sustainability, minimizing detrimental ecological effects and facilitating large-scale, environmentally responsible production of RF-GQDs.

10.5. Long-term stability and potential toxicity

Red fluorescent graphene quantum dots (GQDs) have been extensively studied for their potential applications in biological systems. Their long-term stability and potential toxicity are crucial factors to consider for their successful implementation. Studies have shown that GQDs are susceptible to photodegradation, which can be stabilized in the presence of antioxidants such as reduced glutathione, N-acetylcysteine, or 1,4-hydroquinone, which limit free radical generation and prevent additional chemical changes. Furthermore, the photodegradation of GQDs might alter their physicochemical properties, potentially influencing their biocompatibility and toxicity profiles. Moreover, GQDs can accumulate in red blood cell membranes without affecting cell viability, but they can cause haemolysis,

which is dependent on light exposure and GQD concentration [157]. The toxicity of graphene-family nanomaterials (GFNs) is determined by the following factors: lateral size, surface structure, functionalization, charge, impurities, and aggregates [182]. Studies have revealed that heavy metals, like cadmium, utilized in quantum dots can accumulate in organs including the kidneys and liver leading to toxicity. It is suggested that using carbon-based quantum dots (graphene) rather than metal-based ones could address these problems and provide improved toxicity and biocompatibility results. According to a different study, GQDs did not significantly change in fluorescence qualities for many days, making them a reliable biological marker for stem cells [183].

10.6. Enhancement of stability and toxicity

To combat the challenges of long-term stability and potential toxicity of graphene quantum dots (GQDs) in biological systems, several strategies can be considered. To improve GQDs' stability and decrease photodegradation, and also their efficacy as drug delivery or imaging agents, it is imperative to optimize both their synthesis and surface functionalization. Long-term performance in biological applications can be ensured by minimizing photodegradation by the suitable use of stabilizing agents or antioxidants. Thorough toxicity studies are necessary to assess GQD biocompatibility and comprehend the mechanisms behind haemolysis caused by GQDs. Toxicological concerns can be reduced by using techniques like protective coatings or surface changes. Reliable performance in biological systems is guaranteed by strict quality control measures taken throughout GQD synthesis and characterization. The safe and efficient use of GQDs in theranostic applications necessitates a multidisciplinary approach incorporating material science, biochemistry, and biological research [184].

10.7. Clinical implementation and regulatory authorization

Red fluorescent graphene quantum dots (GQDs), comprehensive long-term studies on their biocompatibility, stability, and potential toxicity are essential. To evaluate their impact on human health, extensive investigations of the biodistribution, pharmacokinetics, pharmacodynamics, and long-term impacts on different cell types and tissues are essential. To assure constant performance and minimize adverse reactions in vivo, physicochemical parameters including size, surface charge, and stability must be thoroughly characterised. Obtaining regulatory authorization requires providing strong preclinical and clinical evidence that demonstrate compliance with strict safety and quality criteria. Translating red fluorescent GQDs from the lab to clinical practice requires cooperation between academics, physicians, regulatory agencies, and industry partners in order to ensure patient safety and regulatory compliance [174].

11. Conclusion and discussions

Among other nanomaterials of the carbon family, GQDs have immense attention owing to its interesting physicochemical properties, tunable bandgap for varying sized GQDs, and excellent photoluminescence behavior, which is made understood by quantum confinement, edge effects (i.e., Armchair and zigzag), additionally due to the presence of oxygen or carboxylic group on the surface; GQDs could attain easily dispersing ability in any solvent type (i.e., polar and non-polar solvents). Furthermore, this article, precisely focused on red fluorescence graphene quantum dots and briefly summarized the definite strategies adopted by researchers to synthesize RF-GQDs, which gives the basic control over size, functionalizing the surface and desired edge type especially emission along with bandgap tunning to attain red fluorescence. The insights of the review critically discussed and reported both top-down and bottom-up approach, also throwing some light on the important characterization techniques, briefing their special properties such as PL tunability, fluorescence mechanism, functionalization, and quantum yield to obtain red emission monitored by band gap tuning and chemical modification. As presented above, on account of its extensive low cytotoxicity, good biocompatibility, deeper tissue penetration, excellent luminescence, good photostability, broad absorption range, and water dispersibility made red fluorescent graphene quantum dots to be outlooked in various applications of the biomedical field. The thorough analysis has additionally commented on the results of in vitro and in vivo analysis of RF-GQDs and it is made evident that RF-GQDs are highly effective for bioimaging, bioprobes and photodynamic dynamic therapy for cancer.

Over the last few years studies have been performed to tune the emission to obtain red fluorescence by tuning its excitation and emission range where the exact reason behind the luminescence is still under research. Although, the poorly understood PL behavior has been validated by the reasonable key factors regulating longer wavelength emission are quantum confinement and bandwidth tunning which provides variable particle size, also doping with chemical groups avails functionalization of surface and relatively extending the emission to longer region, other factors such as concentration dependent emission. Specifically, some reports have also shown that altering concentration of carbon source or solvent with variable pH can emit red shift without any chemical doping. Eventually, RF-GQDs have been exploited to be used in nanomedicine attributing to its intrinsic PL behavior. Presently, the reports on RF-GQDs based biomedical research are evidently increasing by considering its biocompatibility, less cytotoxicity, to absorb and emit in red and near infrared region enabling deeper tissue penetration such characteristics are necessarily responsible for cancer diagnosis involving photodynamic therapy (PDT), photothermal therapy (PTT) as well synergistic therapy (two or more antibiotics or drugs are combined).

Although the strong emission range of GQDs has been the subject of recent research in numerous fields, synthesizing GQDs in a short span has also been the subject of tremendous effects; yet, the reported RF-GQDs also displays some significant challenges. By using various synthesis methods, the desired GQDs structure possibly be altered through chemical modification, where certainly after structural modification complete removal of chemicals should be done. Apparently, this purification process remains complicated,

which requires an ideal purification procedure. Likewise, for practical applications, synthesis process scalability needs to be improved. Despite intrinsic PL characteristics, emission at red and near infrared region experiences lower quantum yield. For biomedical application precisely for bio-sensing, immune-sensing, high quantum yield is highly desired, to which red emissive GQDs are loaded with specialized macrophages as carriers for site-specific delivery, it's also been used as bio-probes or biosensors to detect bio-molecules (DNA, RNA, proteins, genes and nucleic acids) and its changes. Similarly, inherent optical property is indeed important in RF-GQDs based cancer therapy as it requires in-depth tissue penetration. In addition, to validate the performance of RF-GQDs in *in vivo* biological environments; safety, long term toxicity and biocompatibility studies require more focus, to enable therapeutic application. Finally, the complete study summarizes and conclude that GQDs with wider emission window, can be researched and understood more for its rich and inherent properties present and definitely could prove as an asset for various applications with a promising future in advanced technologies and could deliver new perspectives in biomedical and cancer diagnosis (drug delivery and receptor targeted delivery).

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CRediT authorship contribution statement

Shanmuga Priya Mohanaraman: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Ramalingam Chidambaram:** Visualization, Supervision, Project administration, Investigation.

Declaration of competing interest

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

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