



Multifunctional role of carbon dot-based polymer nanocomposites in biomedical applications: a review

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ABSTRACT

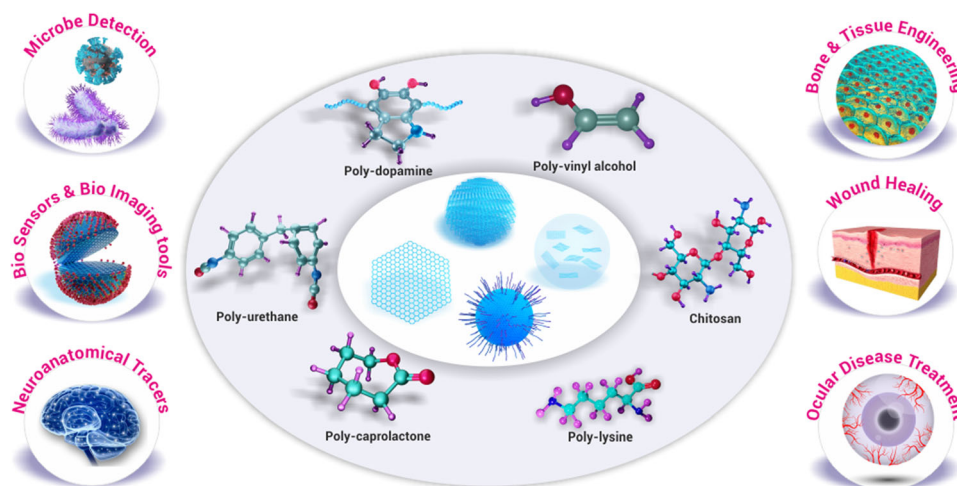
Carbon-based 0D materials have shown tremendous potential in the development of biomedical applications of the next generation. The astounding results are primarily motivated by their distinctive nanoarchitecture and unique properties. Integrating these properties of 0D carbon nanomaterials into various polymer systems has orchestrated exceptional potential for their use in the development of sustainable and cutting-edge biomedical applications such as biosensors, bioimaging, biomimetic implants and many more. Specifically, carbon dots (CDs) have gained much attention in the development of biomedical devices due to their optoelectronic properties and scope of band manipulation upon surface revamping. The role of CDs in reinforcing various polymeric systems has been reviewed along with discussing unifying concepts of their mechanistic aspects. The study also discussed CDs optical properties via the quantum confinement effect and band gap transition which is further useful in various biomedical application studies.

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GRAPHICAL ABSTRACT



Introduction

Polymer composites (PCs) have a wide range of physical, chemical and structural characteristics, which are associated with their application in various fields of science and technology. It includes electronics, robotics and more specifically biomedical sectors due to its amazing features such as reduced toxicity, ease of processing and sterilization, improved shelf life and low weight [1]. However, conventional PCs have certain limitations that restrict their range of applications such as low mechanical strength, and poor antimicrobial and barrier properties [2–4]. Due to the advancement in polymer sciences and nanotechnology over the past few decades, nanomaterial-based PCs, i.e. polymer nanocomposites (PNCs), have shown to be a successful approach to surpassing these restrictions. These PNCs are synthesized when nanosized particles of various shapes and sizes are reinforced into a polymer matrix [5]. However, the reinforcing impact of these nanoparticles is highly dependent on the aspect ratio, size, orientation and dispersion [6]. The reinforcement of these nanofillers ultimately enhances PNC's mechanical, thermal, barrier and flammability properties without compromising their processability

[7, 8]. There are several nanomaterials used for the manufacturing of PNCs including polymer nanofibers, natural clays, metal oxides, metal particles and carbon allotrope-based nanomaterials [9]. Among all, carbon-based nanomaterials (CBNs) are the most extensively studied and used nanomaterials due to their unique properties, applicability and existence in a variety of sizes and shapes [10].

In this context, carbon dots (CDs), a type of CBNs, have drawn a lot of attention as nanofillers in different composites for a variety of biomedical applications due to their extremely small size, outstanding optical properties and biocompatibility [11]. The tale of CDs was started back in 2004 when it was adventitiously obtained by Xu and their teammates during the purification process of single-walled carbon nanotubes (SWCNTs) [12]. After that, in the year 2006, sun et al. originally mentioned the synthesis of CDs by laser ablation of macroscopic carbon material. However, the obtained CDs showed a very low quantum yield (QY) of around 10% [13]. The less QY and challenging synthesis procedures heavily delayed the development of CDs. Later, in 2013, Zhu [14] developed a novel synthesis approach for CD synthesis via a hydrothermal process using citric acid (CA) and ethylene diamine as precursors. The synthesized CD showed the QY up to 80% and was

highest for CBNs at that time. Since then, CDs have evolved swiftly, becoming a cherished topic of research in the realm of material sciences. To tail the development of high-end CDs with high performance, researchers developed various techniques and showed many significant signs of progress in developing the novel CDs including high QYs (> 85%) CDs [15], tunable photoluminescence (PL) with multiple photon emission [16], functionalized polymer dots with high fluorescence performance [17], multicolour or near-infrared emission (NIR) [18] and many more such applications. In recent years, CD-based PNC fabrication and examining their potential use become the contemporary trends in material research. Their combination works as a symbiotic relationship for each other and ultimately strengthens the fabricated PNCs. The polymer matrix maintains a suitable gap between the CDs and restricts their agglomeration. On the other hand, CD improves the optical and mechanical properties of the prepared composites due to its small size, large area and surface revamping capabilities. In the past, few review articles have provided the details of the synthesis methods of CDs, PL mechanisms and their biosensing application and some are also available with the preparation methods and applications of CD–polymer composites [19–25].

This review paper aims to assess and incorporate critical analyses of recent evidences that have not been covered adequately in the contemporary reviews on the CD-based PNCs [26–28]. Feng et al., [26] and Sui et al., [27] gave impetus to the methods of synthesis of CDs while omit discussions on the characteristic phenomenon of quantum confinement and its role in maximizing the potential of CDs. The review by Feng et al. concentrates more on the recent advancement in the green synthesis methods of CDs particularly using organic precursors. Moreover, the review is engrossed in elaborating on energy-based applications of CD-PNCs with a focus on supercapacitor and battery applications [26]. Sui et al., [27] provide a short and summarized account of the properties and applications of CD-based hydrogels while maintaining abstinence from any elaborative-segmented discussions. In a very recent review article, Adam and their co-authors (2022) reviewed the emerging biomedical application of CD/PNCs. It disseminates a critical summary on CDs with the inclusion of short discussions on the advancements in security and agriculture-related applications [28]. The

theme of all these articles is more or less focused on the development, characterization and applications of CDs and their composites and all authors did their job quite phenomenally [19–28]. However, none of them focused on the characteristics and the associated biomedical applications of CD-based PNCs. In this context, the present review article is an effort to fulfil the few shortcomings of the available articles in terms of CD-based PNCs properties and applications. The article also insights into the characteristic properties of CDs which are highly responsible for their biomedical applicability with the polymer composites such as surface revamping and the quantum confinement effect. The review article is a dedicated attempt to provide critical analysis themed on the development of biomedical contrivances with an elaborated discussion on the application of PNCs in bone, scaffold and tissue engineering. Moreover, many areas such as neuroanatomical tracing and wound healing are reviewed which were surprisingly accumulated since their reporting.

Classification and synthesis routes of carbon dots

A quasi-0D CBN with a size less than 10 nm is typically referred to as CDs and broadly classified as graphene quantum dots (GQDs), carbon nanodots (CNDs), carbon quantum dots (CQDs) and carbonized polymer dots (CPDs) (Fig. 1) distinguished-based on their synthesis mechanism, core structure and quantum mechanism [23]. GQDs are disc-shaped nanostructured mostly generated by slicing off the enormous graphene sheets. On the surface/edge or within the interlayer defect, GQDs have one- or multilayer graphite structures connecting chemical groups. They are typically synthesized by “top-down” preparation procedures and exhibit apparent graphene lattices [29]. CNDs are a special type of CD which are having amorphous quasi-spheres without quantum restraints and are often synthesized via bottom-up synthetic techniques. Their cores have a high degree of carbonization but lack any visible crystal structure or polymer characteristics [30]. On the other hand, the CQDs (sometimes referred to as special CND structures) are quasi-spherical structures with a diameter of up to 10 nm. The carbon core of CQDs has a graphitic crystalline structure, and the surface is functionalized by oxygen/nitrogen groups,

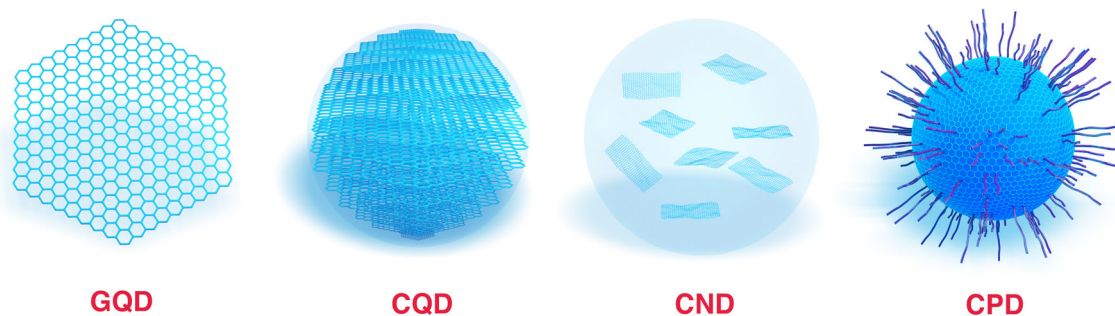


Figure 1 Symbolic representation of different carbon dots.

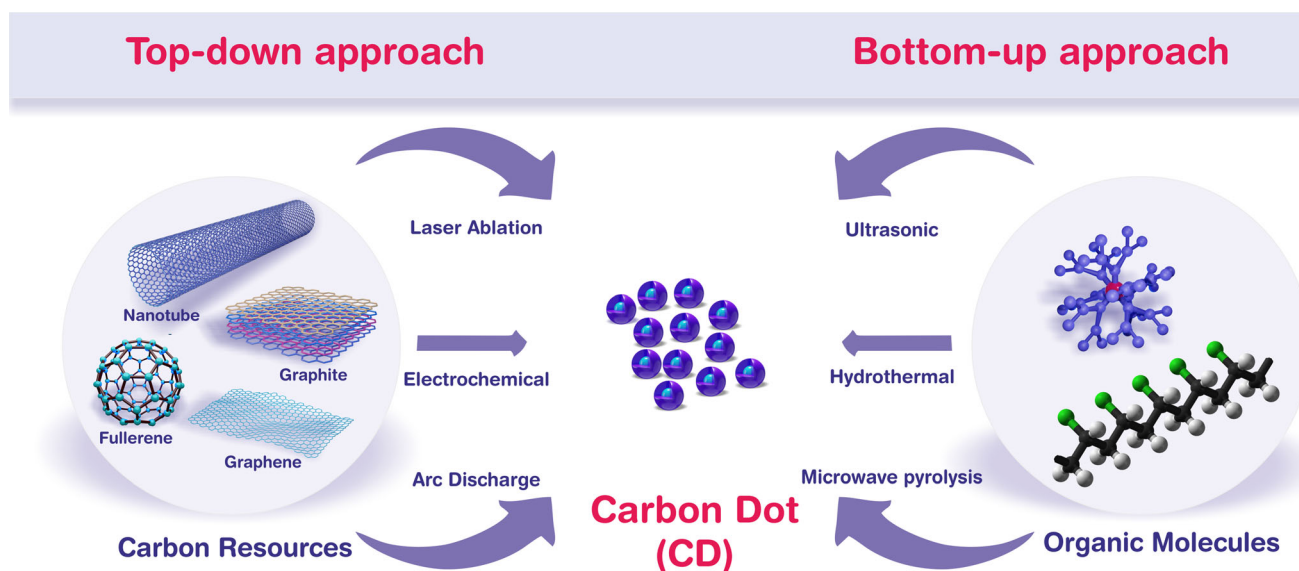


Figure 2 “Top-down” and “bottom-up” synthetic approach of CDs.

which exhibit intrinsic state PL and the quantum confinement effect. As a result, the size of the CQDs and the surface’s functionalization allow for tuning of the PL wavelength [23, 31]. The CPDs, as the name implies, are synthesized by the incorporation of carbonized fragments into a polymer matrix. As a result, the CPDs inherit significant polymeric properties in addition to the characteristics of CNDs. The multi-centre fluorophore structure and unique PL mechanism are thought to be responsible for the CPDs’ ability to display remarkable PL-QYs [16, 32].

Even if CD synthesis methods have been already studied and reviewed in great detail, still it is important to quickly mention the basic synthetic approach as an overture to the topic. The two primary precursors of CDs are natural sources and synthetic sources [33]. However, an in-depth research

is necessary to examine the effect of the employed precursor on the characteristics of synthesized CDs.

Numerous methods can be used to synthesize CDs; however, they can all be categorized into two major groups: “top-down” and “bottom-up” approaches (Fig. 2). These two approaches are a generalized category for the synthesis of all types of CBNs especially 1D-CNTs and 2D-Graphene. In the “top-down” process, the macrocarbon substances (such as graphite, graphene, CNTs and carbon black) break down into smaller one, and in the “bottom-up” approach, small organic molecule (citric acid, polyols, carbohydrate, etc.) synthesizes the CDs via “decomposition–polymerization–carbonization” process [34, 35].

CD-based PNCs and their characteristics

PNCs are multicomponent materials made up of various phase domains, at least one of which is a continuous phase with at least one dimension less than 100 nm [36]. Contrary to conventional carbonized CDs, CD-PNCs show a hybrid structure rather than a core carbon body structure, which contributes to the mostly polymeric surface qualities. As a result, fabricated hybrids have better mechanical and optical properties than non-functionalized CDs and simple polymers. In CD-PNCs, polymers serve as stabilizing agents for high volume-to-surface ratios containing CDs. Polymer structures tend to diffuse through the nanoparticle surface to make up for the famished nature of the CDs surface energy. Typically, CDs can enhance the characteristics or capabilities of the materials currently in use for certain applications. The choice of the polymer matrix (either linear or cross-linked) for the PNC fabrication is based on the desired application. CDs are connected with the polymer matrix only via two types of bonding either covalent or non-covalent bonding. The existing methods for fabricating CD-PNCs may be divided into three categories: physical mixing (solution blending or melt processing), chemical grafting and *in situ*.

Physical blending includes the combination of CDs with the polymer matrix using blending or processing methods. In this process, CDs and polymer matrices are attached via π - π interactions or weak electrostatic bonding [37, 38]. The facile interactions are the main driving factor for producing high-quality PNCs with evenly dispersed CDs when utilizing this approach to manufacture CD-PNCs. Due to the carboxylic group present, CDs often have negative surface charges and prefer to interact with positive-charged polymers. For instance, Pinto et al. created a PNC film utilizing chitosan as the polymer matrix and oxidized CDs from cellulose precursors as a nanofiller. By adjusting the pH value of the prepared hybrid solution, the thickness and shape of the films could be readily controlled [39]. In recent years, many other researchers fabricate CD-PNCs using physical blending processes for various applications [40–43]. This method has the advantages of being low-cost and simple mechanism. But, the self-stacking interactions between CD particles might cause an agglomeration issue that prevents the non-homogeneous dispersion of CDs in the polymer matrix,

leading to poor mechanical strength and lower optical properties. Additionally, because CDs and polymer matrix only interact non-covalently, CD migration from the composite material is also a possibility [44].

Chemical grafting is another significant method for the fabrication of CD-PNCs. The abundance of functional groups on CD surfaces increases the potential for chemical modifications to form covalent bonds with polymers through different reaction mechanisms such as epoxidation, acylation and esterification [45–47]. Due to the covalent bonding between the polymer chains and CDs, chemical grafting is a fairly better technique than blending as the fabricated PNCs are well versed with mechanical strength and optical properties. There are various CD-PNCs are fabricated using chemical grafting. For instance, Erdal et al. [48] fabricated CD-PNCs using polycaprolactone (PCL) as a polymer matrix and nanographene oxide (nGO) produced from cellulose. Ghosh and their teammates [49] grafted the CD-PNC by grafting the surface of CDs with polyaniline (PAni). By oxidizing candle soot with HNO_3 , fluorescent CDs are produced which are further attached to the mono-amine and are used as the key precursor for the oxidative polymerization of aniline in diluted acids. The synthesized CD-PNCs exhibit outstanding electrochemical characteristics. Many other chemical grafting methods are used for the fabrication of PNCs.

Physical blending is the much-favoured way of fabricating CD-PNCs, although this process involves non-covalent bonding which is somewhat unstable and weak. Due to the covalent bond formation, the chemical grafting may effectively bind CDs to the polymer matrix; however, with the several preparation steps, convoluted reaction mechanisms and the involvement of hazardous organic chemicals it is also not without downsides. In contrast, the formation of CDs *in situ* inside the polymer matrix is a simple and environmentally friendly procedure and also the bonding between the CDs and polymer includes both chemical and physical interactions, thus the firmness of the attachment can be better ensured *in situ* synthesis of CD-PNCs is mainly done by using thermal reactions such as pyrolysis or hydrothermal using precursor CDs and polymer solution. In this process, the development of CDs and the construction of PNC happen simultaneously rather than as separate processes [50]. A method for *in situ* synthesis was given

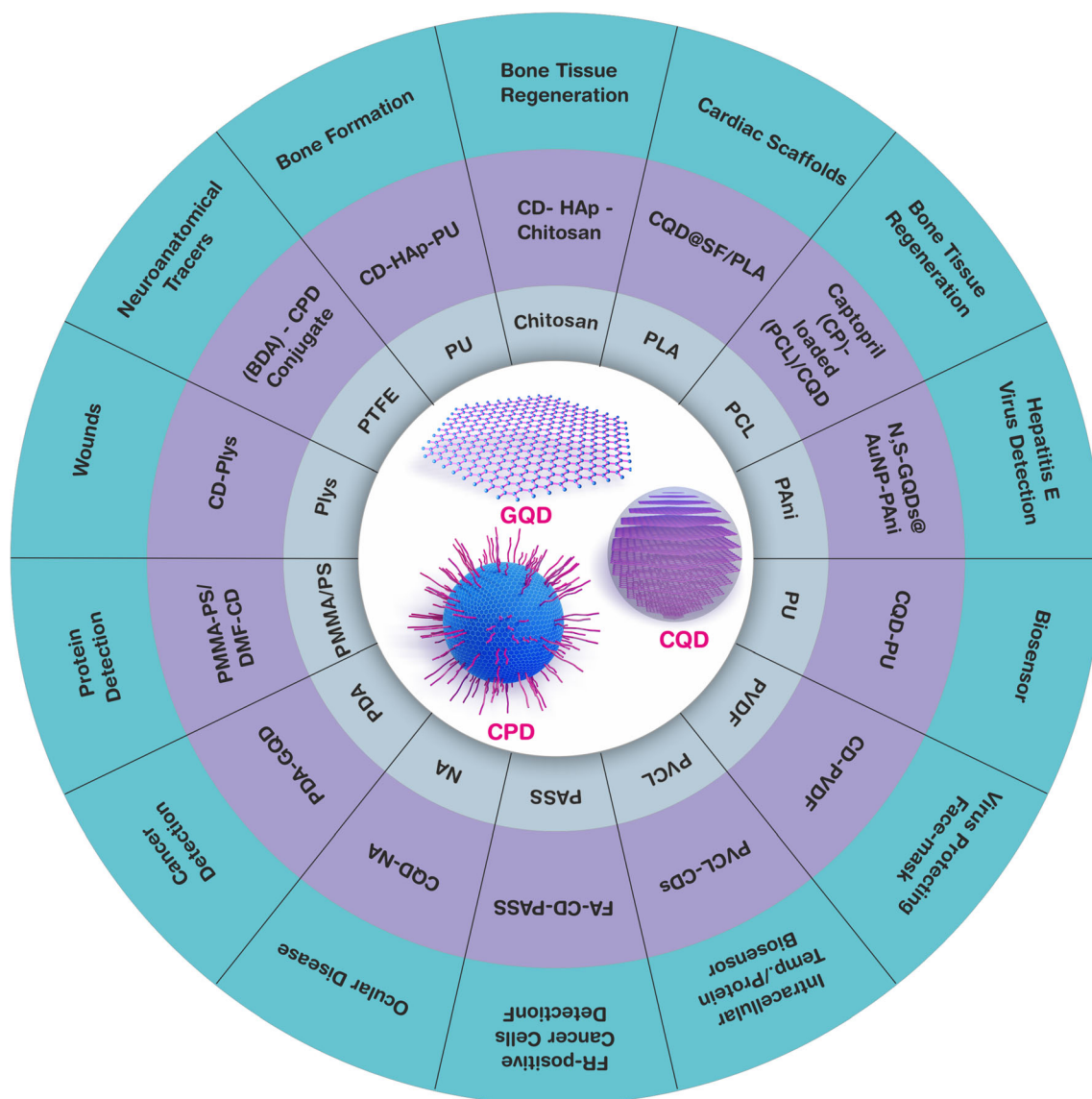


Figure 3 Carbon dots (at core), polymer (inner circle), fabricated CD-PNCs (mid circle) and the associated biomedical applications.

by Fernandes et al., [51] in which pyrolysis of ethanolamine with the polymer matrix (PU, polypropylene, polyethylene glycol (PEG)) was done for the fabrication of CD-PNC fluorescence composite. In addition to this, CDs will directly nucleate and develop on the active sites of the polymer rather than passively becoming trapped there, creating a system that is extremely stable and homogeneous. For example, Lian et al., [52] synthesized a multicolour CD-PU (carbon dot–polyurethane) film for optoelectronic devices. By condensing carboxylated PU in the presence of different carbon-containing components, stretchy, mechanically stable multicolour carbon dot-based films are created. They can interact chemically

with the carbonyl group of the waterborne PU to produce CDs through the amino groups in these compounds. Phase separation would vanish as a result of the CDs and PU becoming a stable and homogenous unit. Furthermore, CD/PU films exhibit remarkable mechanical stability and stretchability in their as-prepared state. Figure 3 displays some common polymers used in the fabrication of various CD-PNCs for different biomedical applications.

Mechanical characteristics

The CD-PNCs are well versed with the three key features: (1) several functional groups attached to the

long polymeric chain, (2) CD homogenous dispersion which enhances mechanical strength and (3) surface revamping which enhances optoelectronic properties. These features provide them with the greater surface, quantum confinement and surface defects, which ultimately increase their physicochemical properties and chances of CD-PNCs applicability for several biomedical sectors such as optoelectronics, tissue engineering and bioimaging.

Different fluorescent CD added to the scaffold (polymers with Hap or other bone-forming components) produces positive outcomes for tissue engineering applications. For the fabrication of scaffolds or in any tissue engineering, the primary criteria are the mechanical properties, because these properties have a significant impact on cell adhesion and proliferation [53, 54]. According to recent studies, the inclusion of CD-PNCs significantly boosted the mechanical characteristics of the scaffold materials. Some of the studies related to mechanical properties are covered in the later part under the biomedical applications and briefly explained here to support the fact that the incorporation of CDs with matrix enhances the mechanical strength of fibre or fabricated bone scaffolds. Gogoi et al. fabricated CD-PU-Hap (carbon dot–polyurethane–hydroxyapatite) composite which exhibits high cell proliferation and alkaline phosphatase activity against MG 63 osteoblast cell line. The prepared composite also exhibits better mechanical properties [55]. Erdal [37] fabricated a nanohybrid using (r-nGO-CA)/PCL: reduced nanographene oxide–caeffic acid–polycaprolactone). The remarkable improvement in storage modulus proves that the carbon nanodots significantly reinforced PCL[40]. Ghorgi [56] synthesized captopril (CP)-loaded polycaprolactone (PCL)/carbon quantum dots for bone tissue regeneration. The composite exhibits excellent mechanical properties and porosity. Recent studies strongly evidence that CD-PNC-based scaffolds are much better for tissue engineering than conventional PC-based composites.

Optical properties: quantum confinement effect and surface modification

The optical features of CD-PNCs have drawn a lot of interest in several biological applications such as biosensing, bioimaging and detection of various life-threatening diseases [57]. This specific property of CD is due to the quantum confinement effect (QCE)

and the surface modulation capabilities. QCE phenomena occur when the size of the CD is very small even smaller than the exciton Bohr radius (it is the separation between electron and hole in an electron–hole pair). When the material's 3D size is reduced at the nanolevel, the valence band and conduction band transits from continuous to discrete energy levels, and the band gap widens, causing a band gap transition in the UV–visible region and significantly increasing the fluorescent QY [58, 59]. Another key reason for the phenomenal fluorescence properties is the surface modulation at the outer core of CDs. The reason for that is the radiation relaxation from a higher energy level to the ground state. The photons whose energy fulfils the optical band gap will transition and gather in the nearby surface defect traps when the light of a certain wavelength illuminates CDs. More surface defects and emission sites on CDs cause higher oxidation which leads to the emission wavelength shifting towards the red [60]. The chromophores or fluorophores that are attached to the carbon backbone of CDs either internally or externally can also emit fluorescence directly.

Due to the QCE and tunable PL, CD-PNCs exhibit a broad-spectrum range and high-intensity emission peaks in the ultraviolet, visible and NIR regions. The CDs emission may be altered by changing the size of the conjugated π -domains. With the increase in the size of conjugated π -domains, the band gap decreases which results to tune the emission from blue to red shift [61]. Different degrees of surface oxidation facilitates the colour-emitting modulation of CDs by changing the band gap between HOMO and LUMO state [26, 62]. The surface chemical groups of CDs have different energy levels, which leads to additional emissive traps in the surface defect states and results in redshift emission wavelengths due to the lower band gap [63]. Figure 4 demonstrates the surface modification via the oxidation process and the associated reduced band gap by which colour modulation can be optimized from the range of blue shift to redshift.

The mentioned features of CD-PNCs are widely used for the bioimaging of cells and tissues. For example, GQD has a nonzero band gap ($T = 0$ K) which can be modified by adjusting the size and surface chemistry of the dots which enhances its applicability as a biosensor with the PNCs [64]. GQDs have been also used as an immune sensor for disease diagnosis based on antigen–antibody (Ag-

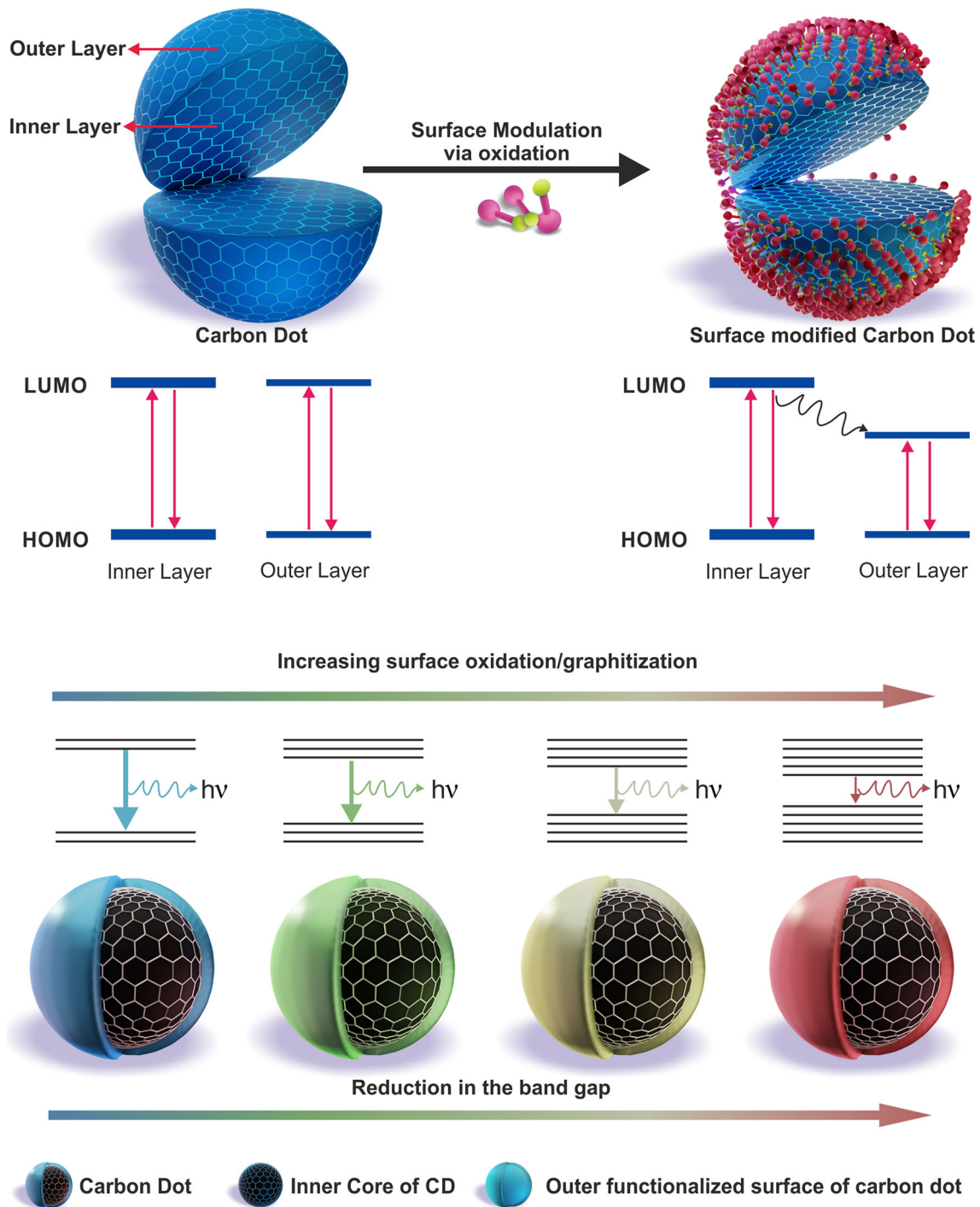


Figure 4 Schematic presentation of surface functionalization in CDs and its impact on the band gap.

Ab) reactions. These immune sensors combine with either Ag or Ab immobilized on the solid substrate, which, upon recognizing the corresponding Ag or Ab, changes the signal [65]. The advantageous structural and compositional synergy of graphene allows GQDs to be an outstanding material for

fabricating various immune-sensing platforms. Various enzyme-labelled antigens have been developed as immuno-sensors amplifying the signals upon the interaction of the Ag-Ab. GQD-based nucleic acid detection platforms have been developed for detecting DNA. It can be used to detect the minute

concentration of DNA due to outstanding biocompatibility and strong fluorescence of GQD [66]. Unlike GQDs, CQDs have a usually spherical core coupled with surface groups. CQDs have found their application in biological imaging due to their broad absorption with narrow emission spectra, large QYs higher molar extinction coefficient and great photostability. A very limited number of GQDs are required to generate the signals during the imaging process because of the extremely stable and bright fluorescence [67]. Additionally, CDs' ability to image deeper tissues is assisted by the reflectance emission feature of NIR, which works in conjunction with low tissue absorption and reduced light scattering in the region of wavelengths greater than 650 nm [68].

Interestingly, CD-PNCs outperform conventional fluorescent dye or semiconductor QDs in terms of biocompatibility and photobleaching resistance. The large surface, high QY and tunable PL make it the most potent nanofiller in PNC fabrication when the motive is to use in biosensing, bioimaging and biodetection. Some of the recent research which is related to CD-PNCs PL properties are explained in the next section with their key biomedical applications.

Applications of CD-based PNCs in the development of biomedical devices

In the field of theranostics, low-dimensional nanoscale materials are being researched more and more for the development of various biomedical contrivances and especially related to sensing and detection. Among the low-dimensional structures, metallic quantum dots (such as MXene QDs, perovskite and TMDCs) attracted much more attention than CDs [69]. But, as we discussed the different aspects of using CDs as a nanofiller in PNC fabrication, it is certainly evident that it will be a much better option among all the QDs in the upcoming years. All these characteristics enhance various advancements in the fabricated CD-PNCs such as reduced toxicity, excellent biocompatibility, tunable PL emission and remarkable photo-induced electron transfer. In Addition, the mechanical and electronic characteristics of CD-PNCs permit covalent and non-covalent conjugation of drugs with nucleic acid or proteins for both diagnostic and therapeutic purposes, such simple functionalization makes it a

beautiful nanofiller for PNCs. All these features of CD-PNCs make them an efficient component in biosensing, bioimaging, phototherapy, bone and tissue engineering, cancer detection, optical imaging, thermo-chemotherapy, wound healing, etc. The various CD-based PNCs are covered in Table 1 with their multifunctional role in biomedical applications and devices.

Neuroanatomical tracing

The neuroanatomical tracing method is used to study and map the complex connections found inside the nervous system. It involves mapping the incredibly intricate connections between neurons contained inside a nucleus or layer of grey cerebral matter, as well as, on a larger scale, connectivity across different parts of the brain [94]. Traditional tracers, however, have several significant drawbacks, including difficult immune histochemical labelling techniques, poor fluorescence intensity and rapid fluorescence quenching. To overcome these difficulties, CDs can be employed as fluorescent material for neuroanatomical tracing.

Zhou and their co-workers [70] experimented with a novel approach in which they use carbon dots as a fluorescent neural tracer for retrograde tracing. The N-hydroxysulphosuccinimide (sulpho-NHS)-modified CDs were conjugated with the cholera toxin B (CTB: a type of protein which is non-toxic cell binding moiety of cholera toxin [95]), i.e. CTB-CDs. Successful conjugation was characterized by the absorption peak at 335 nm. The mass spectrum showed m/z peak of CTB-CDs was 12.0 kDa, and for CTB, it was 11.6 kDa. The calculated z-potential of CTB was around + 3.8 mV due to the high amine group presence, while the z-potential of CTB-CDs, which was conjugated with CDs, was approximately – 17.4 mV due to excess carboxyl groups. In vitro imaging of CTB-CDs was checked by PC12 cell lines and it was observed that CTB-CDs easily distributed in the cytoplasm of PC12 cells without aggregating the cells membrane and nucleus damage. To check the in vivo imaging and tracing ability, CTB-CDs were then injected into the sciatic nerve of the mouse for the fluorescent signal in dorsal root ganglia (DRGs) and spinal segments L3-L5. The findings showed that the CTB-CDs could retrogradely move from axonal terminals to neuronal

Table 1 Representative multifunctional role of CD-based PNCs in biomedical applications

Application	Type of NM	Composite/polymer	Study	Key finding/major outcome	References
Neuroanatomical tracers	NHS-ester-modified CDs	(CTB-CDs) Cholera Toxin B (protein)-conjugated carbon dots	In vitro (PC12)/ in vivo	(Retrograde neuroanatomical tracers) CTB-CDs exhibit significant photoluminescence, optical stability and non-toxicity	[68]
	Carbonized polymer (PTFE) dots	(BDA)-CPD conjugate	In vitro (PC12, RSC96) in vivo	(Anterograde neuroanatomical tracers) BDA-CPDs have superior tracing capabilities as compared to AF594-dextran	[69]
	Carbon quantum dots	CD-HAp-polyurethane	In vitro (MG-63 human Osteoblast cells)	The fabricated nanohybrid composite exhibit excellent cytocompatibility, cell proliferation and alkaline phosphatase activity against MG 63 osteoblast cell line	[52]
	Carbon quantum dots (CQD)	(CS/nHA/CD) Chitosan/nanohydroxyapatite/carbon dots	In vitro/in vivo	The scaffolds improved cell adhesion and osteoinductivity in rat bone mesenchymal stem cells, which significantly improved the formation of vascularized new bone tissue at 4 weeks compared to pure CS/nHA scaffolds in vivo	[70]
Bone and scaffold engineering	Reduced nanographene oxide (r-nGO) carbon nanodots	(r-nGO-CA)/PCL	In vitro (MG-63 human Osteoblast cells)	The excellent cell viability to MG63 osteoblast-like cells showed excellent cytocompatibility of nanodots with the PCL hydroxyapatite (HA) crystals that formed on the surface of the r-nGO-CA loaded nanocomposites exhibited its bioactivity	[37]
	Carbon quantum dots (CQD)	Captropil (CP)-loaded polycaprolactone (PCL)/carbon quantum dots (CQDs)	In vitro (MG-63 human Osteoblast cells)	The synthesized nanohybrid led to a significant increase in the cells' proliferation and Alkaline phosphatase activity (ALP) activity	[53]
	Carbon quantum dots (CQD)	(PCL-PVA-TCP3-CDs)	In vitro Human buccal fat pad-derived stem cells (hBFPSCs)	1.0 wt% of CDs and TCP3 into the PNC showed enhanced cell proliferation and ALP activity	[62]
	Carbon quantum dots (CQD)	SF-CQD-PLA	In vitro H9c2 rat myoblast cells	Enhanced cell viability, adhesion and high young modulus with cardiac marker gene expression	[71]
Skin and tissue regeneration	Carbon quantum dots (CQD)	BC-CQDs-SiNPs-SF and PVA-CQDs-SiNPs-SF	NIH-3T3 fibroblasts	Results showed higher elongation properties, better antibacterial activity and enhancement of NIH-3T3 cell proliferation and migration	[72]
	Carbon dots (CDs)	CDs-CS/GCE	Dopamine detection	The CDs-CS/GCE showed enhanced electrochemical response towards the detection of DA than the GCE	[73]
	Photoluminescent carbon dots	Polydopamine (PDA)	In vitro (Human serum sample)	The sensor exhibited excellent selectivity for the detection of 3-NT in spiked human serum samples	[74]
	Carbon quantum dots (CQD)	SF-CQD-PLA	In vitro H9c2 rat myoblast cells	Enhanced cell viability, adhesion and high young modulus with cardiac marker gene expression	[71]

Table 1 continued

Application	Type of NM	Composite/polymer	Study	Key finding/major outcome	References
	CdTe quantum dots, carbon dots	Chitin	–	ChNF paper assay kits for smartphones are convenient, affordable and portable sensors	[75]
	Graphene quantum dots	N,S-GQDs	–	Successfully prepared electrochemical sensor for hepatitis E virus detection	[76]
	(GQDs)	AuNP-PANI			
	Carbon quantum dots	Polyurethane (PU)	–	From 10 to 90 °C, PU/CDs hybrid films with dual emission displayed temperature response and reversible characteristics	[77]
	(CQD)				
Bioimaging	Nanocarbon dots	Gum tragacanth and chitosan	In vitro	On the MTT test, the carbon dot showed low cytotoxicity and high biocompatibility	[78]
	Carbon quantum dots	Polystyrene (PS) and polymethyl methacrylate	In vitro	DMF-CDs have a lot of potential for biological applications including protein analysis and bioimaging because of their low toxicity and high quantum yield	[79]
	(CQD)				
	Carbon quantum dots	Poly(N-vinylcaprolactam)	In vitro	With an LCST of 33 °C, the aqueous PVCL-CDs solution demonstrated excellent biocompatibility. The product is also used as a bioimaging marker, an intracellular temperature sensor and a quantitative protein biosensor	[80]
	(CQD)				
	Mono-dispersed carbon dots (derived from MWCNT)	Polyvinyl alcohol	In vitro	PL emission covered all the visible regions and not affected by pH alteration (from pH 1 to 11)	[81]
Cancer detection	Graphene quantum dots	Polydopamine (PDA)	In vivo	Better PL stability is displayed by PDA-coated GQDs, which sustain relatively constant over 14 days	[82]
	Carbon dots	FA-CD-PASS	In vitro (HeLa, HepG2 and HEK-293)	The suggested FA-CDs probe is useful for identifying FR-positive cancer cells within mixed populations of normal cells	[83]
		Poly(acrylate sodium) (PAAS)			
	Carbon quantum dots	Ureidopyriminone-conjugated gelatin	In vitro/in vivo	Following exposure to a high concentration of GSH or ROS, the compound demonstrates outstanding adhesiveness and in vivo cancer detection capabilities	[84]
	(CQD)				
	Carbon quantum dots	Polydopamine (PDA)	In vitro	In addition to serving as the gatekeepers for the multiresponsive release of pH, GSH and NIR, the alteration of PDA	[85]
	(CQD)				
Wound healing	Carbon dots	Polyethyleneimine (PEI)	In vivo	CDs also gives the HMC vehicle an exceptional capacity for photothermal production	[86]
	(CDs)			CDs can hasten epithelial cell migration, which results in a quick re-epithelialization of the granulation tissue and the development of the epidermal barrier	
	Carbon dots	Pectin/acryl acid			[87]

Table 1 continued

Application	Type of NM (CDs)	Composite/polymer	Study	Key finding/major outcome	References
	Carbon dots (CDs)	Polylysine (Plys)	In vivo (antibacterial activity in aabbit model)/ in vitro (mice)/ in vitro (MTT assay, antibacterial activity)	The hydrogel showed long-term strong broad-spectrum antibacterial activity because the released CDs significantly damaged the bacterial membrane (even against drug-resistant bacteria) The wounds on CD-Plys healed the fastest, with healing rates of 90% for <i>E. coli</i> and 92% for <i>S. aureus</i> . The synergistic impact of CD31 and Plys, greatly speed up skin wound healing and tissue regeneration	[88]
	Carbon quantum dots	Nucleic acid	In vitro/in vivo	Inhibiting VEGF-stimulated angiogenesis in choroidal blood vessels is efficiently accomplished by hybrid C dots	[89]
Ocular diseases	Carbon quantum dots (CQD)				
Virus detection	Carbonized carbon dots	AS-CDs (<i>Allium sativum</i> derived carbon dots)	Covid 19	Reduced viral attachment and entry while suppressing inflammatory cytokines	[90]
	Carbon quantum dots (CQD)	Poly(vinylidene fluoride) (PVDF)	Face mask	Self-sterilization happens when the membrane receives brief solar radiation because the embedded CDs effectively absorb visible light	[91]

BDA Biotinylated dextran amine; *LCST* lower critical solution temperature; *VEGF* vascular endothelial growth factor; *PVCL* poly(N-vinylcaprolactam); *MTT* 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; *GSH* glutathione; *ROS* reactive oxygen species; *HMC* hollow mesoporous carbon; *NIR* near infrared

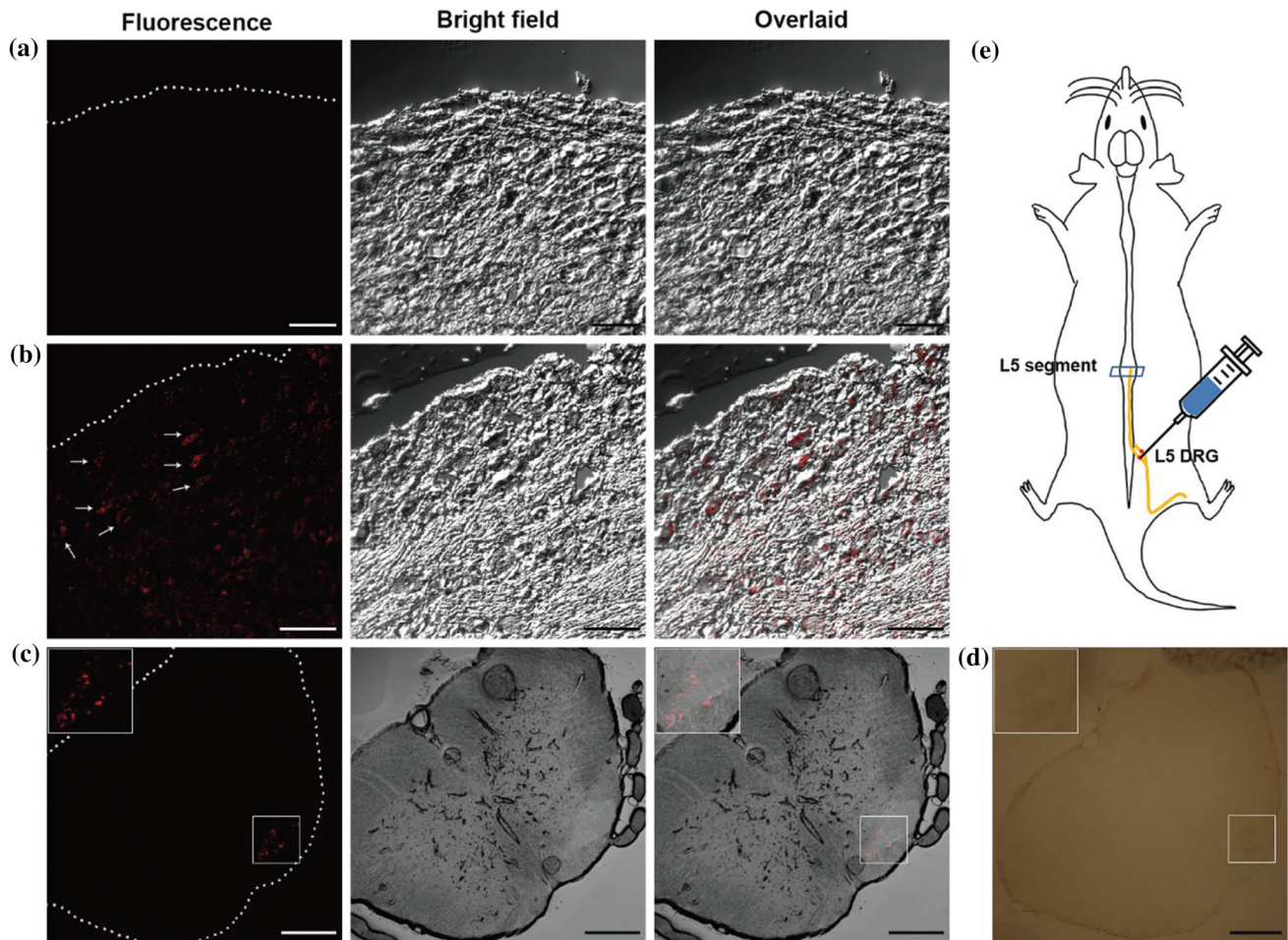


Figure 5 Results of anterograde tracing with BDA-CPD in PNS; L5 spinal segment labelled with saline (a); BDA-CPD (b); labelled primary afferents in the dorsal root ganglion (DRG) of L5 spinal segment with BDA-CPD NCs. Some representative neurons were indicated by white arrows; **d** histochemical staining revealing the

presence of BDA-CPD NCs in DRG; scale bars are 100 μm in A and B, and 500 μm in (c) and (d), (e). Schematic view of rat model demonstrating the injection site and tracing the pathway of BDA-CPD NCs. (Adapted with permission from ref [62] Copyright 2019, Royal Society of Chemistry.

soma in 4 days and could bind to monoganglioside-monosialic acid (GM1) with great affinity.

Liu and their co-workers [62] fabricated a new class of fluorescent nanoneural tracers for anterograde tracing (neuron tracing within the central and peripheral nervous system). The fabrication was done by using carbonized polymer dots (CPDs using polymer: poly(tetrafluoroethylene)) with biotinylated dextran amine (BDA): BDA-CPD. In vitro imaging was checked by using two types of neural cells rat adrenal pheochromocytoma cells (PC12) and rat Schwann cells (RSC96). Similar to AF594-Dextran, BDA-CPDs may quickly disperse within the cells and produce intense red fluorescence. For in vivo, BDA-CPDs and AF594-Dextran were subcutaneously

injected into the backs of naked mice (Fig. 5E). A strong fluorescence signal of BDA-CPDs with a high signal-to-noise ratio was then observed at excitation and emission wavelengths of 570 and 640 nm. In addition, two metabolic routes were also discovered in the in vivo biodistribution of BDA-CPDs which reveals that it can be absorbed and transported anterogradely by a rat's peripheral nervous system (PNS) very efficiently (Fig. 5).

Bone and scaffold engineering

The decent biocompatibility, cellular uptake and low toxicity nature of CDs are used to replace QDs in biological detection and imaging applications. Due to

its spherical shape, it provides a high surface-to-volume ratio and increases the cell–nutrient interaction which makes it suitable as a nanocomposite for bone and tissue engineering [96]. To study the CD's capability as a nanocomposite, Gogoi et al. prepared CD-decorated hydroxyapatite (HAp) implanted in tannic acid and polyurethane (PU) matrix. An elemental study revealed that the Ca/P ratio of prepared nanohybrid was 1.69, which is close to the Ca/P ratio (1.67) of natural bone. A biological study revealed that the fabricated nanohybrid composite showed superior cytocompatibility, cell proliferation and alkaline phosphatase activity against MG 63 osteoblast cell line. These CD-based nanocomposites demonstrated better mechanical properties (tensile strength ~ 20 MPa; elongation at break 221%) and osteogenic activity in studies using MG 63 osteoblasts [55]. The homogeneous distribution of CDs in hydroxyapatite and the cross-linking of CDs and polyurethane are responsible for the scaffolds' remarkable mechanical strength.

Lu et al., [71] investigated the CD impact as a composite in the osteogenesis process. By using a simple freeze-drying technique, they fabricated a unique CD-doped chitosan/nanohydroxyapatite (CS/nHA/CD) scaffold with the potential to support bone regeneration. By up-regulating genes involved in focal adhesion and osteogenesis in vitro, the CS/nHA/CD scaffolds improved cell adhesion and osteoinductivity in rat bone mesenchymal stem cells, which significantly improved the formation of vascularized new bone tissue at 4 weeks compared to pure CS/nHA scaffolds in vivo. Due to the well-known fluorescence property of CDs, the prepared hybrid was also used in tumour photothermal treatment (PTT) using near-infrared (NIR) irradiation (808 nm, 1 W/cm), i.e. CS/nHA/CD + NIR, and showing the excellent capability of killing tumour cells (Fig. 6). The scaffolds successfully stopped tumour development in vivo and greatly reduced osteosarcoma cell proliferation in vitro. Studies showed that CD can potentially be used in PTT treating cancers and infections, as well as enhancing the osteogenesis-inducing capability of bone repair scaffolds.

Erdal et al. [40] also fabricated a nanohybrid using poly(ϵ -caprolactone) and nanographene oxide (r-nGO) carbon dots (PCL) in which caeffic acid (CA) was also incorporated as a reducing agent (r-nGO-CA)/PCL). The study showed that the dispersion of r-nGO-CA

was enhanced by the positive interactions between r-nGO-CA and PCL. The remarkable improvement in storage modulus proves that the carbon nanodots significantly reinforced PCL. The osteo-bioactivity and cytocompatibility of the PCL films containing r-nGO-CA were also assessed. The hydroxyapatite (HA) crystals that formed on the surface of the r-nGO-CA loaded nanocomposites served as a bioactivity indicator. The excellent cell viability to MG63 osteoblast-like cells showed that PCL's good cytocompatibility had been preserved, which bodes well for applications involving bone tissue engineering. Ghorgi et al., [56] synthesized captopril (CP)-loaded polycaprolactone (PCL)/carbon quantum dots for bone tissue regeneration. The results of the nanohybrid showed excellent porosity (for first layer $\sim 80\%$) and decent mechanical properties (tensile strength ~ 22 MPa; elongation $\sim 36\%$). The synthesized nanohybrid led to a significant increase in the cells' proliferation and Alkaline phosphatase activity (ALP) activity. Using CQDs as a nanofiller, Shafiei et al. [72] synthesized PNC made up of poly(ϵ -caprolactone)–polyvinyl alcohol–tricalcium phosphate/carbon dots (PCL-PVA-TCP3-CDs) nanofibrous scaffolds via electrospinning method and checked its osteoconductivity. Results revealed that 1.0 wt% of CDs and TCP3 into the PNC showed enhanced cell proliferation and ALP activity, which in turn increased osteogenic differentiation as a result of CDs and TCP3 working together.

Skin and tissue engineering

Tissue engineering is the procedure of producing bioartificial tissues in a laboratory setting as well as changing how cells grow and function in the body by implanting the right cells, which are extracted from donor tissue, and biocompatible scaffold materials. To encourage the best cell adhesion, motility and deposition of endogenous extracellular matrix components by the cells, biomaterials for tissue engineering must have regulated surface chemistry, porosity and biodegradability. The nanodimensionalities and all the above characteristics make the CBNs the most potent precursor for the synthesis of PNC scaffold materials [97, 98]. Yen et al. fabricated a bioactive PNC scaffold made up of p-phenylenediamine surface functionalized CQD with the silk fibroin/PLA (SF/PLA): CQD@SF/PLA. The micrograph findings showed that the SF/PLA bioactive

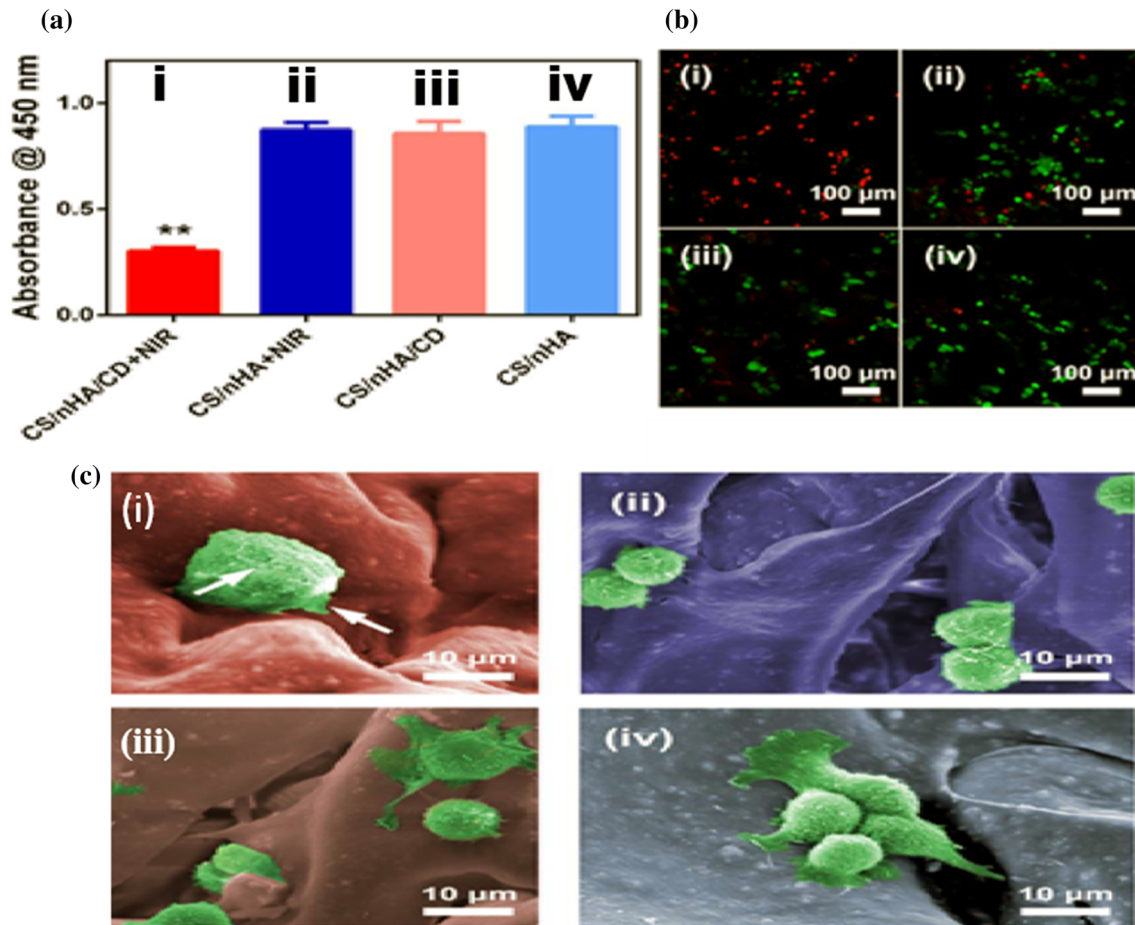


Figure 6 In vitro PTT effect of scaffolds. **a** Scaffolds showing tumour cell killing effect in the presence or absence of laser irradiation. **b** Confocal laser scanning microscopy images of live/dead stained tumour cells (red colour is showing the dead cells which are highest in CS/nHA/CD + NIR group (i.e. symbolized as (i) in each image) indicating the outstanding tumour ablation

effect. **c** SEM image of the tumour cell with different treatments. Tumour cells were swollen and the cell membrane was damaged (highlighted by white arrows) in the CS/nHA/CD + NIR group, whereas they showed normal morphology in the other groups. (Adapted with permission from ref [71]. Copyright 2018, American Chemical Society).

cardiac scaffolds had an equal distribution of the morphologically enhanced spherical functionalized CQD. The fabricated CQD@SF/PLA scaffolds were extremely porous and had uniform pores, which substantially increased implantability, cell adhesion and enhanced young modulus (1610 kPa). The mRNA expression of cardiac marker genes is significantly altered and increased by CQD integration without any electric supply [73]. The study's findings suggested well-organized cardiac nanofibrous scaffolds with improved mechanical and biocompatibility properties for use in cardiac tissue engineering. Abolghasemzade et al. fabricated surface-modified CQDs with bacterial cellulose (BC), polyvinyl alcohol (PVA)-based /silica nanoparticle (Si NP)/silk fibroin

(SF) nanocomposite: BC-CQDs-SiNPs-SF and PVA-CQDs-SiNPs-SF nanofiber for skin tissue and hair regeneration applications. In vivo skin regeneration was accelerated by PVA-CQDs-SiNPs-SF nanofiber (93.3 per cent reepithelization on day 14), which was much faster than BC-CQDs-SiNPs-SF nanofiber (65 per cent), because of its higher elongation property, better antibacterial activity and enhancement of NIH-3T3 cell proliferation and migration [74].

Biosensors

Due to the distinctive properties of modulating the energy gap between their HOMO and LUMO state (as described in Sect. 3.2), CDs are frequently used

with various polymers to fabricate the PNCs for the biosensors. In recent times, researchers synthesize the potential PNCs as a biosensor by using these CDs as a nanoparticle. Huang et al. synthesized a modified glassy carbon electrode (GCE) using CD-chitosan as a PNC: (CDs-CS/GCE) for the determination of dopamine (DA). The study revealed that the GCE performance was electrochemically lower than the CDs-CS/GCE for the detection of DA. With a limit of detection of 11.2 nM, the oxidation peaks current (I_{pa}) of DA was linear with the concentration of DA in the range of 0.1 mM to 30.0 mM. The CDs-CS/GCE was used to successfully detect the presence of DA in an injectable solution of DA [75]. Jalili and Amjadi (2018) fabricated a novel sensor by using polydopamine (PDA) as a receptor in which 3-NT (3-nitrotyrosine) was used as a template and green-emitting CDs as a transducer. Imprinted binding sites that only recognize the target molecules are left in the composite after the embedding template (3-NT) molecules have been removed. 3-NT considerably reduces the fluorescence intensity, which is the basis for its sensitive detection. The CDs and PDA interact with each other via H bonding and/or $\pi - \pi$ stacking. Results showed that synthesized probes have better sensitivity (in μM levels) than many of the HPLC and ELISA methods used for 3-NT detection in human serum samples [76]. Acute hepatitis, a viral condition in which even low levels of the virus represent a potentially lethal hazard, is caused by hepatitis E virus (HEV) infection. Chowdhury et al. described the development of an electrical pulse-induced immunosensor for the impedimetric quantification of the hepatitis E virus (HEV) based on graphene GQDs with co-doped nitrogen and sulphur (N, S-GQDs) and gold-embedded polyaniline nanowires (AuNP-PAni): N,S-GQDs@AuNP-PAni. By altering the electronic properties, the chemically bound nitrogen atom can significantly enhance the electrochemical properties. The target HEV had a large surface area thanks to the AuNP-PAni, which improved the electron transfer process. The biosensing platform easily determined the HEV genotypes with a detection limit of 0.8fgmL^{-1} [78].

Naghdi and their co-workers (2020) prepared a chitin-based nanocomposite fibre (ChNF) optical sensor by using AgNPs (Silver Nps) and AuNPs (Gold Nps) as a plasmonic NPs and CdTe and CDs as colour emitting nanofillers (PLNPs). The proposed ChNF paper-based systems' applicability and

performance for analytical tasks were confirmed by optical sensing of a range of (bio)chemicals as model analytes. Because the synthesized ChNF paper-based sensors are optically transparent, variations in their colour or fluorescence caused by the addition of test analytes may be seen both visually with the naked eye and spectroscopically [77]. Jiang et al., (2020) prepared a hybrid dual light-emitting biosensor through the consistent blending of blue fluorescent polyurethane and green-yellow fluorescent carbon dots (CDs). On the composite film, the CD distribution was rather consistent. After 550 nm in the optical band, the composite film showed a comparatively strong light transmittance of more than 85%. The synthesized film also showed high ductility, flexibility and mechanical stability. The produced CDs' green-yellow emission showed good temperature responsiveness and reversible characteristics [79].

Fluorescence and photoluminescence bioimaging

Bioimaging is a type of optical biosensing method to provide visual images of biological functions or processes for more precise illness diagnosis and treatment. CDs are used for a variety of bioimaging techniques due to their properties of fluorescence and photoluminescence. Morgadi and co-workers (2018) fabricated the photoluminescent nano-CDs via hydrothermal carbonization technique by using gum tragacanth and chitosan as a biopolymer. The prepared composite showed excellent luminescent properties and also showed good photostability with low cytotoxicity and decent biocompatibility on the MTT test [80]. Gu et al., (2018) synthesized the CD DMF-CDs which were easily doped with the polymer matrix of polymethyl methacrylate (PMMA) and polystyrene (PS), the prepared composite exhibited outstanding luminescence stability, superior biocompatibility with the high fluorescence. Under UV radiation (365 nm), the produced CDs released blue light and the quantum yields up to 30%. Results revealed minimal toxicity and high quantum yield, which have significant promise for biological applications such as protein analysis and bioimaging [81].

A carboxyl-terminated PVCL derivative was combined with carbon dots (CDs) through N-(3-(dimethylamino)propyl)-N-ethylcarbodiimide hydrochloride coupling to create a fluorescent thermo-responsive polymer composite PVCL-CD.

The composite temperature-dependent fluorescence characteristics were investigated for biological uses. Due to thermo-induced accumulation of the PVCL chains, fluorescence quenching was seen above the lower critical solution temperature (LCST) in the fabricated PVCL-CDs. These luminous thermo-responsive PVCL-CDs had high biocompatibility and were used as both a marker for bioimaging and a thermometer for measuring intracellular temperatures [82]. The 0D-based PNC film with high luminescence using PVA as polymer matrix and MWCNT-derived monodispersed CDs as nanofillers was synthesized for bioimaging application. In contrast to the pH-dependent fluctuations in photoluminescence intensity often seen for C dots distributed in aqueous solution, the study produced films that display pH-independent photoluminescence (PL) emission, which is a beneficial attribute in terms of biomedical fields [83].

Cancer detection and treatment

CBN's are most frequently researched for their utilization as a nanocarrier in drug delivery. Different methods, such as covalent conjugation or non-covalent adsorption have been developed in recent years to load tiny compounds, such as chemotherapeutic cancer medicines, on CBNs [99]. Besides the nanocarrier, CDs can also be used as a nanofiber in PNCs for cancer detection and treatment. In this context, various studies have been done in recent years. Nurunnabi et al., (2013) evaluated the in vivo biodistribution and possible toxicity of carboxylated photoluminescent GQDs. In vitro analysis of polydopamine-assisted photoluminescent GQDs was assessed against A-549 Cancer cells, MDA-MB231 and MDCK normal cell line. The optical imaging of naked mice and isolated organs showed that 24 h after intravenous injection of GQDs, carboxylated GQDs accumulated in the liver, spleen, kidney and tumour. Blood biochemistry and haematological studies exhibit that the carboxylated GQDs do not appear to be hazardous to rats at different dosages (5, 10 mg/kg) over 22 days [84]. Liu et al. developed a one-step synthesis of green fluorescence carbon dots (CDs) with poly(acrylate sodium) (PAAS). A unique turn-on fluorescence probe was developed for imaging cancer cells via the hydrogen-bond interaction between folic acid (FA) and CDs: (FA-CDs). Study findings indicated that the FA-CDs probe could

reliably identify cancer cells that expressed the folate receptor (FR) in various cell mixes when turned on. Particularly, the targeting of FA-CDs probes and the superb photostability of CDs have enormous implications for real-time tumour cell monitoring and fluorescence-assisted surgical excision [85].

Cancer detection and healing mechanism were also checked using diselenide-containing carbon dots (dsCDs) and ureidopyriminone-conjugated gelatin (Gel-UPy) hydrogels by formulating stimuli-responsive electrochemical wireless hydrogel biosensors. The creation of hydrogen bonds, which have an impact on the self-healing capacity, conductivity and adhesiveness of the Gel-UPy/dsCD hydrogels, is triggered by the cleavage of the diselenide groups of the dsCD inside the hydrogels by glutathione (GSH) or reactive oxygen species (ROS). Due to the deterioration of dsCD, the breakage of diselenide bonds also impacts the electrochemical signals. A high concentration of GSH or ROS causes the hydrogels to demonstrate outstanding adhesion and in vivo cancer detection abilities [86]. In another study on PNCs, a photothermally improved multifunctional system (MFS) was formed using the NIR-absorbing agent polydopamine (PDA) and carbon dots (CDs). Both were gated on the apertures of hollow mesoporous carbon (HMC). It was observed that the prepared MFS's fluorescence emission wavelength was red-shifted by the Förster resonant energy transfer (FRET) interaction between PDA and CDs, which eliminated the problem of fluorescence quenching in CDs and made cell imaging easier. Modification with PDA@CDs not only makes the multiresponsive release of pH, GSH and NIR, but it also gives the HMC vehicle outstanding photothermal generating capacity, the ability to conduct bioimaging and improved stability [87].

Wound healing

Wounds arise more frequently from accidents, surgeries, burns and chronic illnesses and exaggerate by the microbial infection occurred due to the various pathogens. Due to their unique physicochemical and biological characteristics, CBNs demonstrated broad antimicrobial activity against invasive bacteria, fungi and viruses causing wound infection [100]. Wang and their co-workers (2020) studied the CD's effectiveness against wound infection. By stimulating the transforming growth factor- β /p-38 mitogen-activated

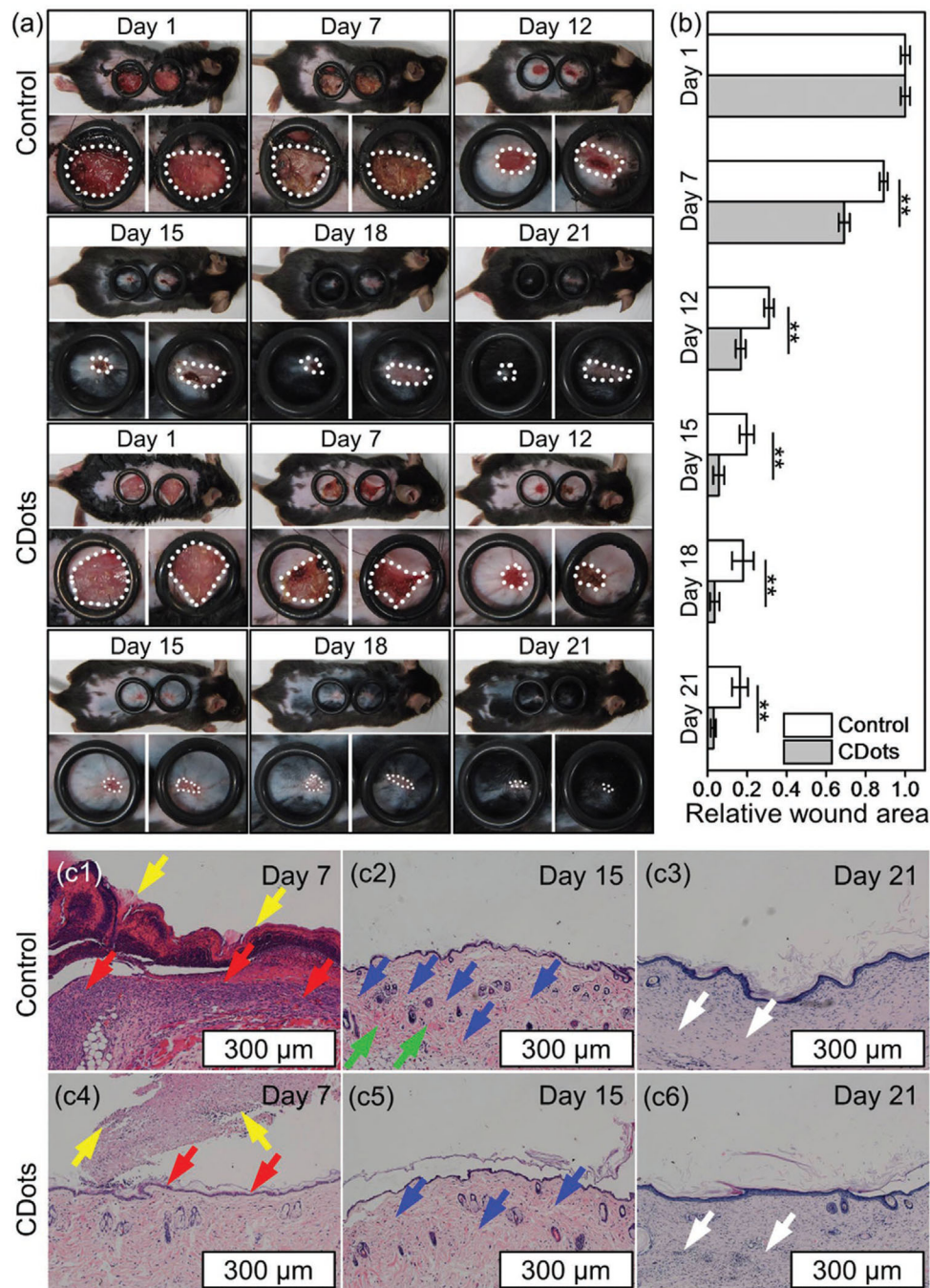


Figure 7 In vivo wound healing and histological assessment **a** Images of cutaneous wounds on different days. **b** Relative Wound area (ratio of the wound area of different time points to the initial wound area) on different days treated with control and CDots. **c** Histological evaluation on days 7, 15 and 21. Yellow arrows: scabs; red arrows: inflammation and epithelium; blue arrows: collagen fibres; green arrows: hyalinization; white arrows: scars. Adapted with permission from ref [88]. Copyright 2020, John Wiley and Sons.

kinase/Snail signalling pathway, the CDs cause the epithelial-mesenchymal transition (EMT), which increases cell motility. The study also demonstrated that CDs can speed up epithelial cell migration in

full-thickness cutaneous wounds through EMT by evaluating several in vivo wound healing tests and histological exams (Fig. 7). As a consequence, the granulation tissue and epidermal barrier are rapidly

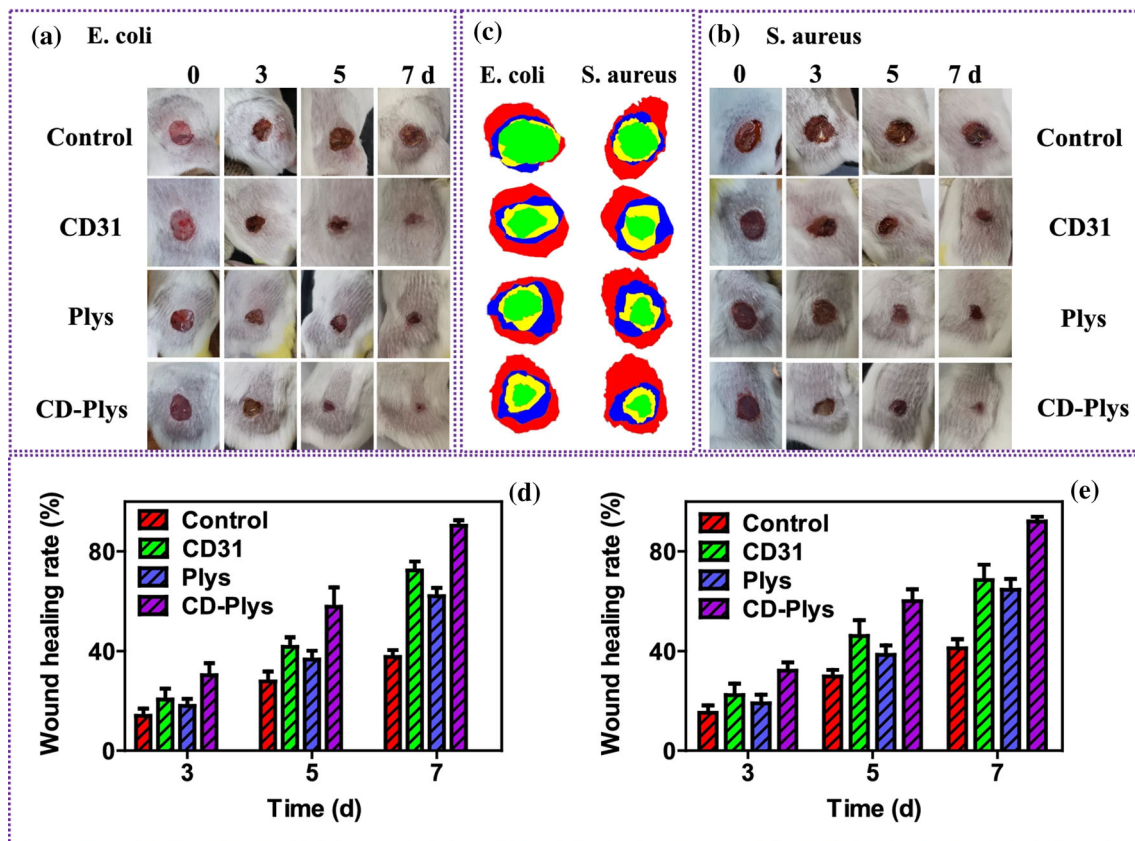


Figure 8 In vivo wound healing evaluation. **a** and **b** are images of *E. coli*- and *S. aureus*-infected wounds on different days treated with different hydrogels (Control, CDs, Plys and CD-Plys). **c** Traces of wound during 7 days of treatments (0 days: red pattern; 3 days: blue pattern; 5 days: yellow pattern; 7 days: green pattern). **d** and **e** are wound healing rates (%) of *E. coli* and *S. aureus* wounds on different days. (Adapted with permission from ref [90]. Copyright 2022, Springer Nature Society).

re-epithelialized, blocking external stimuli, reducing the inflammatory response and granulation tissue area, and ultimately promoting wound healing with fewer scars [88].

Cui et al. (2021) fabricated cationic carbon dots (CDs), acrylic acid (AA) and pectin network by a cross-linker which worked as an effective fluorescent hydrogel with antibacterial efficacy, phenomenal optical performance and excellent biocompatibility. Due to the bacterial membrane being severely disrupted by the released CDs, the hydrogel demonstrated long-term powerful broad-spectrum antibacterial efficacy (even against drug-resistant bacteria). This hydrogel's inhibition capacity was 108.5 times more than that of the other hydrogel [89].

Mou et al., (2022) developed a group of anionic CDs, particularly CD31, into effective broad-spectrum bactericides. Additionally, CD31 was coupled with polylysine (Plys) to create an injectable, self-

healing hydrogel (CD-Plys) that has outstanding wound healing capabilities, amazing broad-spectrum antibacterial activity and satisfying biocompatibility (Fig. 8). The in vivo study results that the size of the wound rapidly decreased in the CD-Plys composites as compared to the pristine plys. The epidermis started to regenerate only after 3 days of treatment and on the 7th day, the CD-Plys showed remarkable healing up to 90 and 92% for *E. coli* and *S. aureus*, respectively. The results showed that the synergistic impact of CD-Plys promotes angiogenesis and epithelization, which ultimately speeds up wound healing [90].

Other biomedical application

The CD-PNCs are also used in several other applications which are less studied in comparison with the above biomedical applications, for instance ocular

disease. Pathogenic angiogenetic eye illnesses are brought on by the vascular endothelial growth factor (VEGF). Developing carriers for the regulated release of VEGF inhibitors that are located in the rear of the eye region is a difficult scientific task. Shoval et al., (2019) synthesized the hybrid CDs functionalized with the VEGF aptamer. When applied topically, the CDs serve as efficient transporters of the anti-VEGF aptamer throughout the cornea. Because of the CDs' natural fluorescence, the hybrids also allow for non-invasive intraocular concentration monitoring. They exhibit no toxicity in both in vitro and in vivo mouse animal models. Additionally, choroidal blood vessels with the hybrid CDs significantly block VEGF-stimulated angiogenesis [91]. The viral illness COVID-19 mostly affects the lungs and results in severe respiratory distress and fever. Globally, a recent epidemic has caused a significant number of fatalities due to this virus. Since immune cells produce mediators like interleukins, which cause inflammation after the virus connects to receptors and attacks lung cells [101]. For the rapid determination of the virus, CDs can be employed for the pandemic COVID-19 diagnosis and therapy. Herbal CDs, i.e. made from the carbonization of medicinal plants, can play a vital role as potent anti-COVID-19 agents. Kalkal et al. synthesized CDs via carbonization using *allium sativum* (AS) as a biomaterial. CDs derived from garlic reduced viral attachment and entry while suppressing inflammatory cytokines [92]. However, the study was hypothetical and has not yet been tested in vivo or in a human patient. But, the low toxicity, enhanced cell viability and cytocompatibility suggested that by preventing the spread of illness, AS-CDs can aid with preventative measures. The suggested theory can be used as a forward-looking strategy to pave the way for the creation of a unique treatment that may prove to be very effective in dealing with such pandemics. In addition, CD-PNC systems are also used for the fabrication of facemasks due to their excellent quality of inhibiting viruses. Additionally, CD-PNCs can also be used for the fabrication of high-end quality facemasks. Singh et al. created CD–poly(vinylidene fluoride) (PVDF) nanoporous membranes and their potential for usage in reusable, self-sterilizing facemasks. Notably, the composite CD-PVDF films have a hydrophobic surface that avoids moisture build-up and a dense nanoporous network that permits efficient filtering of particles larger than 100 nm in diameter while yet allowing for breathability.

Importantly, self-sterilization happens when the membrane receives brief solar radiation because the embedded CDs effectively absorb visible light while simultaneously raising the temperature through heat dissipation [93].

Challenges and opportunities

With the rise in the structural analogues of CBNs, an exponential upturn has been seen in the fabrication of smart polymer composites. The CD-PNCs also exhibit such characteristics and applications which make them one of the most suitable nanocomposites for the fabrication of several biomedical devices as we discussed in the application part of this review. The synthesis methods, biocompatibility, environment-friendly nature and optical properties make CDs a vital nanomaterial for several applications. It is evident from several studies that the CDs are the most biocompatible and low toxicity-containing CBNs. Among all its physicochemical characteristics, one of the most important nature is its tunable PL property which is very useful in the biomedical sector from cancer detection to biosensor fabrication. The study of CDs in terms of their synthesis, properties as well as mechanistic research and application development, has advanced significantly. The findings of these studies show that CDs can offer a variety of unique opportunities to examine novel phenomena and features discovered in multifaceted settings. However, there are still several challenges associated with CD-based nanocomposites which need to be resolved for better future opportunities of the CDs in material science and technology.

The studies on CDs and their properties are quite stagnant in their earlier stages when compared to other QDs and other CBNs (such as CNTs or graphene). The lack of an appropriate and scaled method to generate high-quality CDs with required morphology (such as shape, type, size, number of defects and functional groups) is now one of the most basic and significant challenges. Due to the unconventional synthetic routes, their precise reaction mechanism, reactivity or response towards the other functional group molecules are also not clear. Therefore, the effects of precursors and reaction conditions on the performance of CDs should be systematically explored, and a purification strategy based on size or polarity also needs to be developed,

to produce CDs on a large scale with high performance via an efficient route.

Owing to the various reaction mechanisms and precursors used by several researchers, the PL mechanism of CDs is still up for debate. The key factors influencing their PL behaviours include the structures of their carbon cores and the attachment or bonding of different functional groups on their surfaces (as shown in Fig. 4). However, there are no clear pathways for optimizing the PL properties of CDs which is one of the major hindrances to using CDs efficiently for the fabrication of CD-PNCs composites, especially for biosensors. Hence, to facilitate the synthesis of CDs with high QYs and tunable PL mechanisms, it is important to thoroughly evaluate the structure and investigate the PL processes of CDs by combining experimental studies and advanced computer techniques. Besides the PL issue, the other concern is to synthesize the CD as per their applicability. Future studies should concentrate on creating CD structures in accordance with application needs in addition to synthetic approaches and the PL mechanism.

In the biomedical field, the CD-based PNCs showed enhanced selectivity in different sensing and imaging applications due to the functional polymer attached to the surface of the CDs. So, there is also a need to develop a more convenient and appropriate approach for the synthesis of CD-based PNCs. For potential future clinical applications in phototherapy and smart medical devices (such as health monitoring gadgets, brain mapping systems, neural tracers and cancer-detecting sensors), CD's red to NIR radiation is highly desirable due to its reduced dispersion and less damage to the tissues and deeper light penetration. So, there is also a need to create such multiphoton emitting CDs which have high QYs, biocompatibility and outstanding water solubility. All these properties can alter the nature of a polymer composite in multiple dimensions. For CDs to be used in therapeutic in the future with polymeric systems, a thorough study on the toxicity and metabolic pathways of PNC-based CDs in animal models is much needed and also a thorough investigation of the precise molecular mechanism of drug/PNC-CDs is necessary.

Conclusion

This review paper attempts an elaborative discussion on the fabrication and applications of the CD-based innovative composite structures. It emphasizes the

mechanistic understanding of the synthesis, fabrication and properties of reinforced polymer nanocomposites. Inferences have been made based on an extensive literature survey based on the representative literature with significant results. The substantial findings reported in this article insinuate the immense potential of CDs in the development of biosensors and bioimaging tools. The structural remodelling and extraordinary tuneable PL emission properties can be harnessed for the development of several significant devices, materials for bone and tissue engineering, tracers, biosensors or disease detection. It is anticipated that the novel method of synthesis and alterations through doping and polymer conjugation will play a key role in the field of biological sciences for the development of futuristic novel biomedical contrivances. This review article can be seen in the backdrop of a suitable compact and rational literature for the inception of several CD-based research endeavours, especially in biomedical applications.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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