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Effect of carbon nanodots on the cellular redox reaction and immune system

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Carbon nanodots are ultra-small carbonaceous nanostructures with excellent photoluminescence and cytocompatibility properties, making them suitable for developing excellent bioimaging probes. They exhibit dual properties, generating and scavenging reactive oxygen species, and are used as photosensitizers to produce reactive oxygen species under light and as photothermal agents that transform light energy into heat. This makes it possible to use them in photothermal and photodynamic therapies to treat cancer. They may enter the body by various means, including inhalation, ingestion, or intravenous injection. Once inside, they travel through the bloodstream, infiltrating tissues where they come into contact with the immune system, similar to infectious agents. These nanodots are identified by several receptors on the surface of innate immune cells, such as monocytes and macrophages, which attempt to engulf these nanodots. This interaction can induce a pro-inflammatory (M1) or anti-inflammatory (M2) response, modulating immune activity. This review explores the immuno-toxic potential of carbon nanodots, focusing on their ability to modulate redox balance by catalase, glutathione peroxidase, and superoxide dismutase, which are examples of antioxidant enzymes. Although carbon nanodots have demonstrated a wide range of applications, their effect on the cellular immune system remains largely unexplored. In this study, we primarily addressed the sophisticated impacts of carbon nanodots on the immune system and their diverse processes, such as the many cellular redox reactions implicated in antibacterial and antiviral treatment, wound healing, drug administration, and tumor therapy. As a result, we outline the benefits and difficulties of carbon nanodots in the biomedical domain and discuss their potential in the future development of clinical medicine.

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1. Introduction

One of the most prevalent elements in the universe is carbon. Carbon has a surprising variety of allotropes. The carbon family of nanomaterials (CNF) consists of carbon nanofibers, carbon nanodots (CNDs), nanotubes, nanodiamonds, graphene, and fullerene, as shown in Fig. 1. CNDs are a well-known functional nanomaterial recently found to have superior qualities.[1] CNDs are zero-dimensional, discrete, tiny fluorescent quasi-spherical nanocrystals with a size of less than 10 nanometres (nm). These materials, owing to their excellent properties, including

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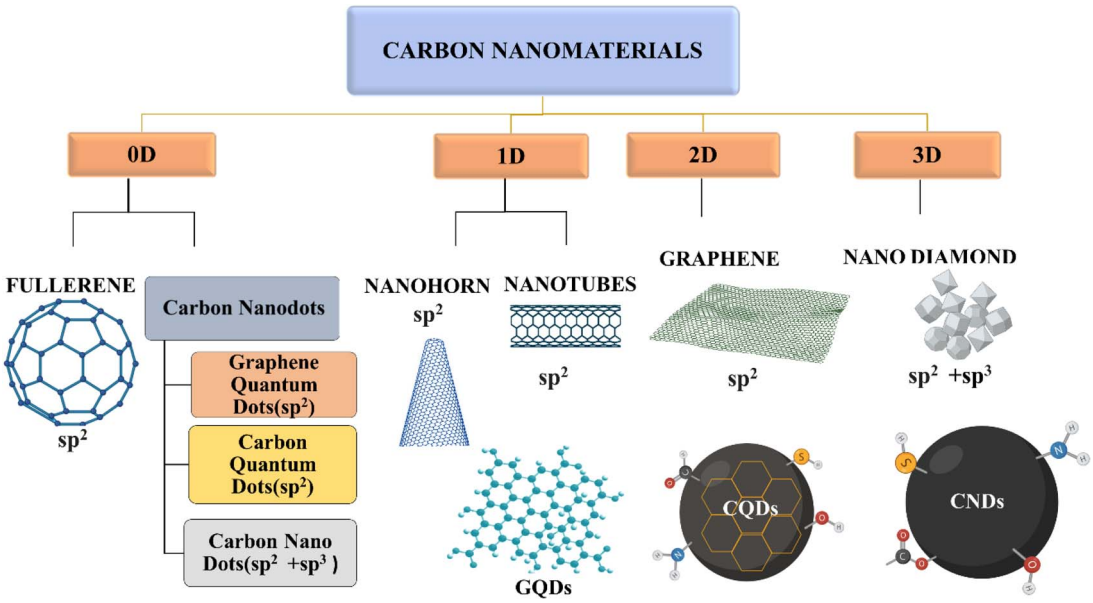

Fig. 1 The diagram illustrates the classification of CNDs based on their dimensions, structural features, and bonding. Carbon nanomaterials are classified into several categories based on their dimensionality: zero, one, two, and three-dimensional. Again, 0D is classified into fullerene (sp^2) and carbon dots (sp^2 and sp^3), 1D is classified into nano-horns (sp^2) and nanotubes (sp^2), 2D is classified as graphene (sp^2), and 3D is classified into nanodiamonds (sp^2 + sp^3). This classification highlights their structural versatility and potential applications in technology and biomedicine.

hydrophilicity, robust chemical inertness, easy modification, good biocompatibility, and low toxicity, and tuneable properties like optoelectronic features, especially high intrinsic fluorescence, along with their biosafety and composition and functionalization modification, made easy, are of broad scientific interest.[2]

CNDs exhibit amorphous and surface defects and oxygen-containing functional groups, including hydroxyl, carboxyl, and epoxy groups, because surface oxidation happens during production. These groups disrupt the sp^2 hybridized carbon network, resulting in surface defects. Surface passivation involves adding a protective layer to CNDs to enhance stability and extend their shelf life. The passivation layer shields CNDs from exposure to impurities and environmental factors.[3] Their flaws, surface ligands, edge shape, and size affect their photoluminescence (PL) characteristics. Many heteroatoms, including metals (Zn, Mg, Ag, Au, Cu, Ga, *etc.*) and sulfur (S), nitrogen (N), boron (B), and phosphorus (P), can be doped with CNDs that effectively enhance the physiochemical and optical properties of CDs.[4] This technique also alters the electronic states in the carbonic framework structure and surface chemistry of the CNDs. The lowest unoccupied molecular orbital (LUMO) and highest orbital (HOMO) levels can be changed by doping.[5]

The "top-down" and "bottom-up" approaches are two major approaches for synthesizing CNDs.[6] CNDs exhibit remarkable versatility, functioning as photosensitizers that generate ROS under light exposure and act as scavengers without light. Specifically, the ability of CNDs to modulate oxidative stress and interact with the immune system presents promising avenues for therapeutic interventions. Their antioxidant capabilities can protect against oxidative damage, while their ROS-generating potential under controlled conditions can be harnessed for targeted therapies. Understanding the mechanisms through which CNDs influence cellular redox states and immune responses is crucial for developing novel treatments for diseases associated with oxidative stress and immune dysregulation. Because CNDs are both electron donors and acceptors, their applications as prooxidants or antioxidants depend on the activity of the unpaired valence electrons. It has been claimed that several tests based on the nitrogen-centred 2-2-diphenyl-1-picrylhydrazyl radical (DPPH) have been employed to confirm their antioxidant function.[7] Research suggests that carboxyl groups on the surface of CNDs, which can operate as proton donors and convert DPPH into a stable DPPH-H complex through a hydrogen atom transfer (HAT) process, are the primary source of the antioxidation of CNDs. However, evidence

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suggests that carboxyl groups do not directly contribute to CND antioxidation.

In this review, the main focus is the impact of CNDs on cellular redox reactions and the immune system, highlighting their potential therapeutic uses and the challenges in predicting their behaviour due to their structural variability. Research on CNDs continues to expand, particularly focusing on their potential in biomedical applications such as drug delivery, bioimaging, anti-inflammatory effects, tumor therapy, antimicrobial therapy, and wound healing, and their impact on the immune system. Their ability to interact with biological systems, combined with their low toxicity and tunable properties, positions them as a promising tool for developing antioxidant therapies and managing oxidative stress. This versatility and broad applicability make CNDs a subject of considerable scientific interest, with ongoing studies exploring new functionalization and applications.

2. Structure of CNDs

CNDs have various surface functional groups, as shown in Fig. 2. These functional groups provide CNDs with high hydrophilicity, facilitating their use with biological, inorganic, polymeric, and organic substances.[8] CNDs have amorphous structural features and are made of graphene and graphene oxide sheets bonded together by diamond-like insertions. They have core–shell structures that can be either amorphous (mixed sp^2/sp^3) or crystalline (sp^2), depending on the amount of sp^2 carbon in the core. The crystalline cores are typically small, around 2–3 nm, with a lattice spacing of about 0.2 nm. The core type depends on the synthesis method, precursors, and other parameters like temperature, duration, and pH.[9] Many characterization techniques, such as transmission electron microscopy, X-ray diffraction, Raman spectroscopy, nuclear magnetic resonance, and X-ray photoelectron spectroscopy, have been pivotal in studying the core structure.[10] The degree of ordering or crystallinity is evaluated by Raman spectroscopy; CNDs usually exhibit D and G bands, which correspond to defects and graphitic sp^2 carbon, respectively, at D (~1345 cm^{-1}) and G (~1585–1600 cm^{-1}), respectively. These bands' intensity ratio (I_D/I_G) reveals crystallization levels. A higher D/G intensity ratio indicates more structural defects in the carbon core due to the pentagonal and hexagonal rings. The primary functionality of CDs is oxygen-containing, *i.e.*, carboxylic acid moieties that act as a substrate for simple functionalization and water.[11]

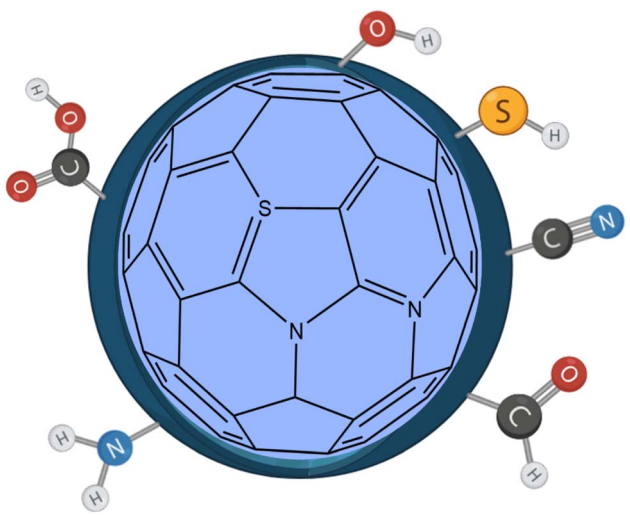

Fig. 2 Schematic representation of carbon nanodots (CNDs) illustrating their core–shell structure, while the surface has various functional groups (*e.g.*, –OH, –COOH, and $–NH_2$) that enhance stability, biocompatibility, and functionality.

CNDs exhibit unique structural features that make them multifaceted and functional nanomaterials. These features include their π-conjugated domains and the abundance of edge and defect sites, which play an important role in defining their optical, electronic, and chemical properties.

2.1. π-Conjugated nature

The state of the CND system also affects the distance between the CNDs and the fluorescence quenching mechanism. The π-conjugated nature of CDs arises from the presence of sp^2-hybridized carbon atoms arranged in aromatic structures embedded within an amorphous sp^3-carbon matrix. These conjugated domains allow for the delocalization of π-electrons, leading to well-defined electronic and optical properties.[12]

2.2. Edge and defect sites

CNDs have abundant edge and defect sites due to their small size. So, these structures enhance their optical and chemical properties. Edges of the CNDs are highly reactive and typically functionalized with oxygen-containing groups (–COOH and –OH) or heteroatoms (N and S). These functional groups improve solubility, biocompatibility, and the ability to conjugate with drugs. The fluorescence of CNDs can be tuned by using defects, particularly those caused by oxygen-related functional groups at the edges. A higher oxygen content increases the defects, leading to a more pronounced red shift in fluorescence.[13]

Additionally, the chemical composition of CNDs differs according to the synthetic technique used. Xu *et al.* (2004)[14] discovered that the CNDs during the electrophoretic purification of single-walled carbon nanotubes from arc discharge shoots. Their composition was 53.93% carbon, 2.56% hydrogen, 1.20% nitrogen, and 40.33% oxygen.[15]

3. Properties of CNDs

3.1. Chemical properties

CNDs have distinct chemical properties. For example, GQDs are anisotropic particles consisting of one or more graphene layers with edge functionalization. However, CNDs are distinguished into amorphous (spherical) carbon nanoparticles and crystal lattice-containing CQDs.[16] Functional groups are added to the surface to improve electron transport characteristics and surface interactions with other molecules, which are advantageous for catalysis and sensing. CNDs are less toxic than other nanoparticles because they do not contain toxic metals (like

lead and cadmium).[17] Due to high surface reactivity, many conventional nanoparticles (metal oxide and quantum dots containing heavy metals) can generate ROS during cellular uptake. However, CNDs have low reactivity due to their stable carbon core. Also, many functional groups (–OH and –COOH) help scavenge the ROS rather than generate them.[18]

3.2. Electrochemical properties

CDs have special electrochemical properties that make them ideal for various electrochemical applications. These properties include a large surface area, which increases electrical conductivity through electron–hole pair formation. They are also low-cost and less toxic, making them economical and environmentally friendly.[19] Additionally, heteroatom doping, such as with sulphur, can improve electronic properties by promoting intramolecular charge transfer and providing reactive sites for electrocatalysis. The electrochemical properties of CDs are influenced by their size, surface functionalities, and heteroatom doping. For example, smaller GQDs exhibit higher specific capacitance and more efficient power response.[20]

3.3. Optical properties

Optical properties include absorbance, photoluminescence, and phosphorescence, as shown in Fig. 3.

3.3.1. Absorbance. It is used to obtain information about the chemical structure of the CDs. Typically, absorption peaks correspond to transitions between π–π* and n–π* in the core. CDs have significant UV absorption that reaches the visible and near-infrared spectra.[21] In the UV-visible spectrum, CQDs typically show two absorption bands between 280 and 350 nm in length, combined with a large tail in the ultraviolet range. An absorption band at 280 nm results from a C=C bond's π–π* transition, whereas the one at 350 nm results from a C=O bond's n–π* transition. Surface passivation or modification can affect the absorption characteristics of CQDs.[22]

3.3.2. Photoluminescence (PL). PL is the optical phenomenon that occurs when a material absorbs a photon of light and emits a photon as soon as one of its electrons transitions from a higher electrical excited state (S_1) to a lower energy state (S_0). There are two types of photoluminescence: the first is fluorescence, and second is phosphorescence.[23]

3.3.3. Fluorescence. The fluorescence of CNDs is significantly influenced by their surface state, which includes surface oxidation and functional groups. Oxygen-related groups can introduce surface defects, leading to various emission sites on the CDs and surfaces, enhancing fluorescence. More surface defects increase the trapping of excitons, resulting in red-shifted emission due to the recombination of trapped excitons.[24] The fluorescence of CNDs can be tuned by using defects, particularly those caused by oxygen-related functional groups at the edges. A higher oxygen content increases the defects, leading to a more pronounced red shift in fluorescence.[25]

3.3.4. Phosphorescence. The phosphorescence properties of CNDs, especially long-lifetime room-temperature phosphorescence (RTP), have attracted attention. Achieving RTP requires enhancing spin–orbit coupling, often by adding transition metals and minimizing non-radiative transitions. Polymer CNDs, with cross-linked structures, are promising RTP materials due to increased intersystem crossing and suppressed non-radiative transitions. Heteroatom doping can accelerate the intersystem crossing process by promoting the n–π* transition of C=O and C=N, for example, with phosphorus, nitrogen, and halogens.[13]

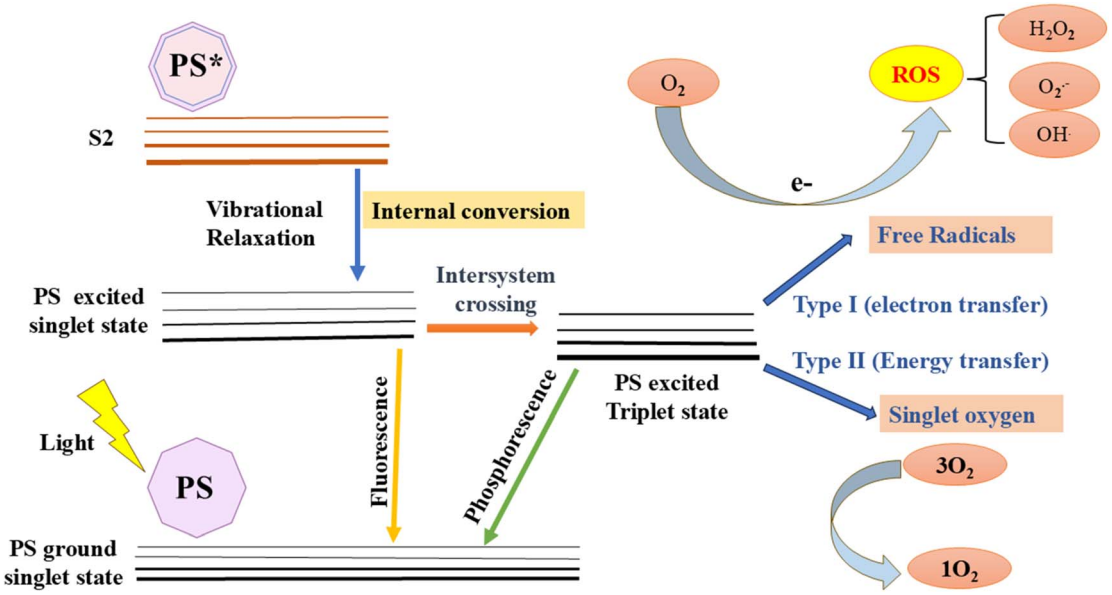

Fig. 3 Schematic diagram of photodynamic therapy including the Jablonski diagram. In this diagram, the PS initially absorbs a photon that excites a singlet state and this can relax to a triplet state. This triplet state interacts with the oxygen in two pathways, type I and type II, leading to ROS and singlet oxygen formation, respectively. Both ROS and singlet oxygen can damage pathogenic microorganisms like bacteria and viruses. ROS is also effective in anticancer, antiviral, and antimicrobial therapy.

Table 1 Classification of doping and its effect on CNDs

Type of doping	Dopant elements	Effects on carbon nanodots	Quantum yield	Preparation method	Ref.
Non-metal doping	Boron (B)	Improves optical properties, enhances conductivity, and enhances phosphorescence and fluorescence properties	39.4%	Hydrothermal	31
	Sulphur (S)	Introduces new functional groups, and Fe^{3+} detection enhances catalytic properties and enhances the electronic properties of the carbon dots	67%	Hydrothermal	32
	Nitrogen (N)	Enhances photoluminescence quantum yield, increases surface active sites, and improves water solubility	81%	Hydrothermal	33
	Phosphorus (P)	It enhances electrical conductivity, introduces additional active sites, contributes to the photoluminescence properties of CNDs, and enhances stability and biocompatibility	16.1%	Hydrothermal	34
	Selenium (Se)	Excellent antioxidant properties	81%	Hydrothermal	35
Metal doping	Copper (Cu)	Enhances optical activity, improves catalytic activity, and leads to high ROS production	9.81%	Hydrothermal	36
	Zinc (Zn)	Enhances electron transfer, photoluminescence quantum yield, and Hg^{2+} detection	48%	Hydrothermal	37
	Cerium (Ce)	Enhances wound healing, shows antioxidant activity, and PL properties	93.14%	Hydrothermal	38
	Ag (silver)	Good antibacterial properties	38.4%	One-step process	39
Co-doping	N, S co-doping	Improves charge separation, and enhances catalytic activity	24%	Microwave-assisted/microwave-assisted solvothermal	40
	N, P co-doping	Enhances electron transfer properties and improves biocompatibility	22.14–92.1%	Hydrothermal	41
	B, N co-doping	Improves optical properties and increases surface functional groups	32%	Simple hydrothermal carbonization method	42

3.4. Doping

Doping is an effective method for modulating the intrinsic properties of CDs. Introducing atomic impurities such as N (Fig. 2), P, and B into CDs can alter their electronic structure to generate n-type or p-type carriers, as explained in Table 1. This modifies the PL properties of carbon dots that enhance the quantum yield.[26] The main purpose of doping is to enhance CDs' functionalities and luminescence properties.[27] However, metal doping has the potential to make CNDs more hazardous. Thus, non-metal doping is recommended because it is non-toxic and has a simple production method.[28] CDs doped with various non-metal heteroatoms, including Si, S, N, and B-doped CDs, have expanded their uses in bioimaging and multi-target detection.[29] CDs' photoluminescence quantum yield (PLQY) is an essential parameter in the above applications, and it can vary greatly. The PLQY is mainly dependent on the CD synthesis process and chemical composition, yielding values as low as less than one percent to more than 90%.[30]

4. Synthesis

Precursors like synthetic and natural polymers are a major source of CNDs. The different types of precursors used to synthesize CNDs significantly impact their performance. Heteroatom-rich precursors containing sulfur, nitrogen, or phosphorous (such as urea, thiourea, or ammonium salts) are effective at doping CNDs. Heteroatom precursors improve redox activity and catalytic efficiency.[43] On the other hand, aromatic precursors like aniline derivatives enhance the π–conjugated structure of CNDs. Natural precursors including orange peel, lemon juice, soy milk, chitosan, *etc.* can be used to synthesize CNDs.[44,45] Amino acids such as cysteine or lysine have nitrogen and sulfur compounds suitable for applications involving modulation of immune responses. So, tailoring or combining these precursors makes it possible to synthesize the desired CNDs for successful immune cell interaction and managing oxidative stress. The methods used to synthesize CNDs are "top-down" and "bottom-up" techniques, further explained in Table 2.

4.1. Top-down method

Graphene, ash, or soot are examples of big carbon precursors broken down to produce nanosized particles in the top-down method of creating CNDs. Top-down techniques include electrochemical oxidation, laser ablation, arc discharge, and oxidative cracking.[46]

Table 2 Methodologies for preparing CNDs with advantages, limitations, properties, and applications

Synthetic methods	Advantages	Limitations	Characteristics/ properties	Applications in CNDs	Ref.
Top-down approach					
Chemical exfoliation	Large-scale manufacturing, and simple procedure	Harsh conditions, drastic processes, multiple steps, and poor control over sizes	High surface area and broad size distribution	Biosensors, drug delivery, and bioimaging	47
Laser ablation	Fast, effective, and morphology and size control	Low quantum yield, poor control over sizes, and sophisticated process	High purity, tuneable size, and high photoluminescence	Fluorescent tags, bioimaging, and optoelectronic devices	48
Ultrasonic-assisted treatment	Easy operation	Instrumental wastage and high energy cost	Easy to scale up and high dispersion	Pollutant detection and water purification	49
Bottom-up approach					
Microwave	Size is easily controlled, size distribution is consistent, and reaction time is quick	High cost of energy	High yield, eco-friendly, and rapid synthesis	Photocatalysis and energy storage	50
Hydrothermal	Inexpensive, non-toxic, and superior quantum yield	Low yield	Simple process and water-dispersible	Chemical and biological sensors	51
Solvothermal	Cheap and non-toxic	Ineffective size control	Solvent-based, tuneable surface properties	Fluorescent probes and cellular imaging	52
Pyrolysis/Carbonization	Simple to use, solvent-free, inexpensive, and capable of large-scale manufacturing	Non-uniform size distribution	High thermal stability and solvent-free	Supercapacitors and batteries	52
Chemical vapor deposition	High yield, and controlled size and shape	Complicated operation and high cost	Precise control over structure and high purity	LED devices and transistors	53

4.2. Bottom-up method

Using carbon precursors, which are tiny organic molecules and polymers with –OH, –COOH, and $–NH_2$ functional groups, the bottom-up method produces CNDs. The typical process is carbonization after dehydration, which produces CNDs with homogeneous morphology, narrow particle size dispersion, and stable characteristics. Synthesis of CDs *via* a bottom-up approach involves solvothermal, pyrolysis, hydrothermal, and microwave synthesis, among other techniques.[46]

5. Cellular redox reaction and oxidative stress

5.1. ROS dynamics in CNDs, and its generation and scavenging mechanisms

CNDs have properties that generate and scavenge ROS. ROS is a highly active molecule that contains oxygen and singlet or triplet electrons like hydroxyl radicals (OH^-), superoxide (O_2^-), and non-radical molecules like H_2O_2.[54] CNDs generate ROS through external stimuli or agents that induce oxidative stress. Cancer cells have higher levels of ROS than normal cells and maintain homeostasis by activating antioxidant pathways. ROS can be both beneficial (cell signaling and defense mechanism) as well as harmful (causing oxidative stress and cellular damage). Thus, generating ROS by means of external stimuli like a photosensitizer, sono-sensitizer, and ionizing radiation, and inducing oxidative stress in cancer cells, is a promising approach that helps to treat cancer cells.[55] Li *et al.*[56] highlighted the antioxidative properties of selenium-doped carbon quantum dots (CQDs) and graphene quantum dots (GQDs). These nanomaterials can stabilize radical species by forming adducts, donating hydrogen ions, and transferring electrons. However, this antioxidative activity reduces ROS generation, compromising the effectiveness of photodynamic therapy (PDT) and chemo-dynamic treatment (CDT). To overcome this limitation, it is necessary to develop CDs with combined photodynamic and chemo-dynamic functionalities to enhance their potential in ROS-based therapeutic applications. Combining the ROS-generating agents with chemotherapy then makes cancer cells more susceptible to these treatments. If we increase the oxidative stress, the cancer cells will weaken.[57]

PDT involves the energy absorbed by a photosensitizer (PS). A PS is a chemical compound that exhibits light-sensitive chemical reactions when exposed to light. The main components of PDT are PS, visible light, and oxygen. These all are individually harmless but when combined, produce potent ROS.[58] CNDs have conjugated double bonds containing a delocalization of the π-electrons. In the PS ground singlet state electrons are spin-paired in low-energy orbitals. When a PS is exposed to light, the PS is excited from the lowest unoccupied molecular orbital (LUMO) to the highest occupied molecular orbital (HOMO). The most crucial process for PDT is the intersystem crossover, which is the reversal of the excited electron's spin and results in the triplet state of the PS. According to the Pauli exclusion principle, the excited electron, now with a spin parallel to its previous paired electron, may not instantly return to a lower energy level, and hence this triplet state is less

energetic than the excited singlet state but has a significantly longer lifespan (microseconds as opposed to nanoseconds). Accordingly, the excited electron in the PS triplet state may interact with molecules abundant in its immediate environment, or it may change its spin orientation (a somewhat slow process) and expel its energy as phosphorescence. The PS triplet may react readily with molecular oxygen, and is one of the few molecules that are triplets in the ground state; due to these selection rules triplet–triplet interactions are permitted but triplet–singlet interactions are prohibited.[59]

Molecular oxygen (O_2) is necessary for PDT to create ROS. The ground electronic state of oxygen is a triplet, as was previously described. This triplet can undergo energy transfer upon collision with the excited PS triplet because its two outermost orbitals are unpaired but spin parallel. In this type II process, the outermost O_2 electron's spin is "flipped" and shifted into the orbital holding the other electron, leaving one orbit completely unoccupied (a violation of Hund's law). This type of oxygen, singlet oxygen ($^1O_2$), is very reactive and short-lived due to its unstable electron configuration. Type I is an alternative photochemical process that occurs when the PS triplet directly transfers an electron. The proton donation to O_2, producing superoxide anion $O^{\bullet 2-}$, which can further produce ROS, such as hydrogen peroxide (H_2O_2) (Fig. 3).

The type I process produces ROS with various distinct reactivities. Perhaps the most reactive of the three ROS produced, OH is a potent electrolyte that may chemically target multiple biomolecules. $O^{\bullet 2-}$ is the least reactive, whereas H_2O_2 is less reactive. Nevertheless, superoxide dismutase may convert $O^{\bullet 2-}$ to H_2O_2 and O_2. Only when H_2O_2 combines with ferrous iron in a process known as the Fenton reaction is it regarded as really reactive.[60]

$$H_2O_2 + Fe^{2+} \rightarrow OH^- + {}^{\bullet}OH + Fe^{3+}$$

ROS generation and scavenging depend on the presence and absence of light sources for antitumor and antibacterial therapy, and wound healing. ROS-scavenging antioxidants are used to treat diseases. ROS can be generated using a PS under specific light, known as PDT. PDT treats various cancers like oesophageal, lung, and skin cancer.[61] PDT and sonodynamic therapy (SDT) are non-invasive methods; in SDT, ultrasound energy sources generate ROS for therapeutic effects. Tao *et al.* synthesized CND-based nanoclusters prepared by combining manganese-doped CNDs with a sonosensitizer, hematoporphyrin monomethyl ether, and hyaluronic acid coating. Under ultrasonication, these nanoclusters promote antibacterial activity and break down the biofilm. It accelerates healing in infected wounds by removing biofilms, decreasing inflammation, and improving tissue repair, making it an feasible approach to anti-infection therapy.[62]

Antioxidants and photosensitizers were explored in various clinical applications but faced several challenges. Therefore, new antioxidants and photosensitizers are needed to regulate ROS levels effectively.[63] Some diseases like cancer and chronic wounds require ROS generation and scavenging in different tissue parts. Various nanomaterials, including carbon nanomaterials, Fe_3O_4 nanoparticles, and gold nanocages, have shown high antioxidant or pro-oxidant activities.[64]

5.2. Mechanisms of CND-induced oxidative stress

Oxidative stress occurs when there are high levels of ROS inside cells, leading to oxidative damage to lipids, proteins, and DNA.

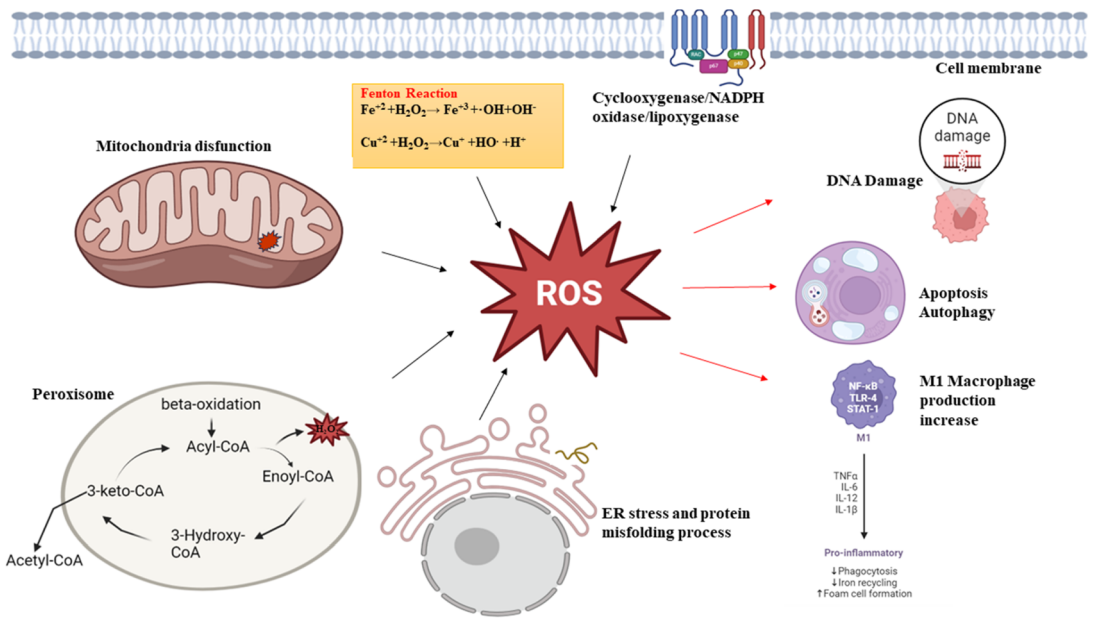

Fig. 4 Internal production of ROS. The electron transport chain generates ROS in the mitochondria, the main source of intracellular ROS. The unfolded protein response in the endoplasmic reticulum (ER) is mediated by protein disulfide isomerase and xanthine oxidoreductase in peroxisomes. Transmembrane NADPH oxidases are also responsible for ROS generation. All of these lead to DNA damage, apoptosis autophagy, and increase the production of M1 macrophages.

Table 3 Different redox signaling pathways and their impact on CNDs

Redox signalling pathway	Impact	Mechanism	Applications	Ref.
MAPK pathway	Cell proliferation and stress response	ROS generated by CNDs activates MAPKs, leading to phosphorylation and JNK, and p38 MAPK, ERK activation	Cancer treatment, (apoptosis), proliferation, differentiation, and inflammatory response	71
NF-κB pathway	Apoptosis, inflammation, cellular adhesion, and autophagy	By blocking I-κB alpha phosphorylation, CND-generated ROS activate the NF-kB pathway and allow NF-κB to translocate to the nucleus, activating target genes	Anti-inflammatory therapies and immune response enhancement	72 and 73
Pathway PI3K/AKT	Control hallmarks of cancer, including cell growth, survival, and metabolism	ROS influences the activity of PI3K and AKT through oxidative modifications	Metabolic disorder treatment, enhancing cell survival, and cancer treatment	74
Nrf2 pathway	Antioxidant response	Oxidative stress brought on by CNDs causes Nrf2 to separate from Keap1 and activates genes involved in antioxidant defense	Antioxidant therapies and protection from oxidative damage	75
HIF-1 pathway	Cellular response to hypoxia	CNDs affect the stability and activity of HIF-1 under oxidative stress, influencing gene expression related to angiogenesis and metabolism	Targeting tumor hypoxia and enhancing adaptation to low oxygen	76

Numerous diseases are linked to this stress. However, ROS also plays a role in normal cell functions by acting as signaling molecules in redox biology.[65] ROS is also known as a strong antioxidant that defends against CNDs. It is believed that the ability of CNDs to donate electrons is connected to their capability to scavenge free radicals, even if the precise mechanism underlying these antioxidant properties is yet to be understood.[66] The massive surface area of CNDs comprises carboxyl, hydroxyl, and amino functional groups, which are assumed to be responsible for oxidizing and reducing these free radicals.[67]

ROS are produced mostly in the mitochondria but can also be found in other organelles, including the peroxisome and the endoplasmic reticulum (ER), and by transmembrane NADPH oxidase and Fenton reaction which are explained in Fig. 4. However, because an imbalanced generation of ROS may cause harm to cells, oxidative stressors are accountable for several significant disorders, including cancer, neurological diseases, and inflammation. Excessive ROS levels disturb the cell balance, which can provide an efficient antioxidant response, known as oxidative stress. Even though ROS may be harmful to cells, they may be produced under control and utilized in PDT, antiviral, and antibacterial applications.[66]

There are some reactions for the production of ROS.[68]

• One of the most reactive anions, superoxide anions ($O_2^{\bullet -}$), is produced when molecular oxygen is reduced.

$$\text{CNDs} + h\nu \rightarrow e^- + h^+$$

$$O_2 + e^- \rightarrow O_2^{\bullet -}$$

• Molecular oxygen and H_2O_2 are produced when $O_2^{\bullet -}$ is dissimulated.

$$2O_2^{\bullet -} + 2H^+ \rightarrow H_2O_2 + O_2$$

• Partial reduction of H_2O_2 gives hydroxide ions (OH^-) and the radical hydroxide ($^{\bullet}OH$)

$$H_2O_2 + e^- \rightarrow HO^- + {}^{\bullet}OH$$

$$2H^+ + 2e^- + H_2O_2 \rightarrow 2H_2O$$

5.3. Intracellular redox signaling pathways affected by CNDs

The effect of CNDs on intracellular signaling pathways like MAPK, NF-κB, and PI3K/AKT pathways has shown significant potential in biomedical applications. Cell proliferation, differentiation, and stress response can be controlled through the MAPK signaling pathway. ROS generation occurs when CNDs are introduced into the body, which further activates MAPK signaling. Furthermore, depending on the level of ROS, this may promote cell apoptosis (*via* P38 MAPK) or cell survival (*via* ERK). A research group developed ginsenoside Rg-1 carbon nanodots for treating human lung cancer. Inducing ginsenoside Rg-1 CNDs activates the expression of MAPK pathway-related proteins. These CNDs exhibit high inhibitory effects on proliferation, migration, and pro-apoptotic ability in lung cancer A549 cells. Rg1 CNDs successfully promoted tumor apoptosis and could be considered a therapeutic agent for

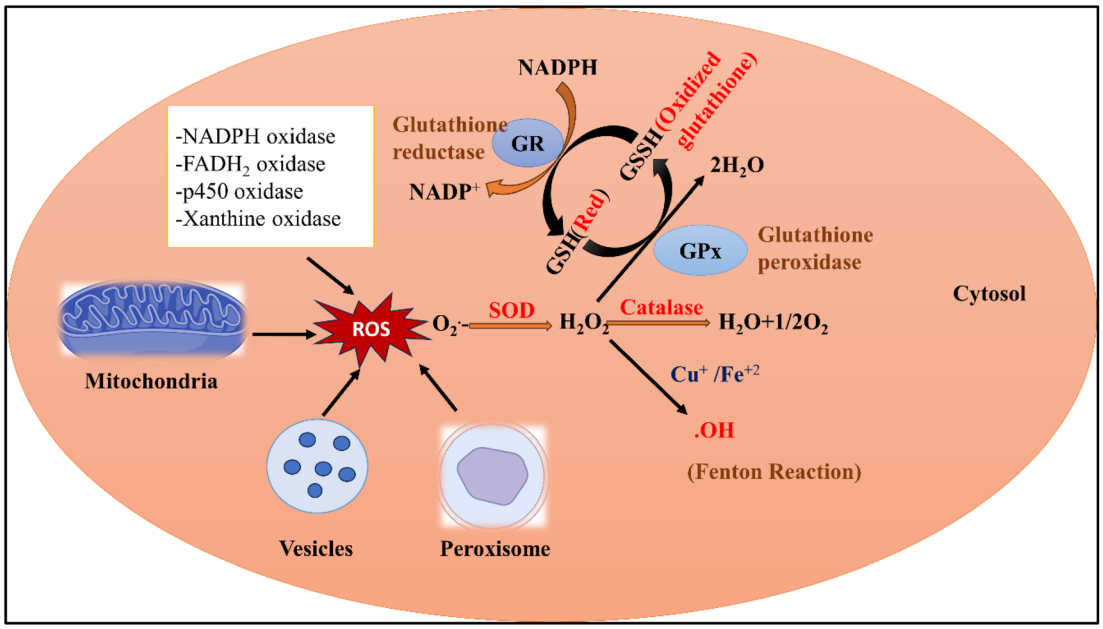

Fig. 5 The primary antioxidant enzyme's coordination with the production of ROS within cells. Superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) work together to protect cells from oxidative damage. SOD converts superoxide radicals into hydrogen peroxide, and catalase then helps to maintain physiological levels. However, under pathological conditions, redox-active metals such as copper and iron can facilitate the formation of hydroxyl radicals from hydrogen peroxide through the Fenton reaction. GPx reduces hydrogen peroxide to water, using reduced glutathione (GSH) as a substrate and converting it to its oxidized form, glutathione disulfide (GSSG). Glutathione reductase (GR) then regenerates GSH from GSSG, playing a crucial role in the cell's redox defense mechanism.

Table 4 Antioxidant enzymes and molecules: functions and responses to CNDs

Antioxidant defence	Function	Response to CNDs	Mechanism	Reaction	Ref.
Superoxide dismutase (SOD)	Produces H_2O_2 and O_2 from superoxide radicals ($O_2^{\bullet -}$)	Increased activity	Reduces superoxide radicals generated by CNDs, protecting cellular components	$2O_2^{\bullet -} + 2H^+ \rightarrow O_2 + H_2O_2$	80
Catalase (CAT)	Converts H_2O_2 into oxygen and water	Upregulated activity	Prevents formation of hydroxyl radicals by breaking down H_2O_2	$2H_2O_2 \rightarrow 2H_2O + O_2$	81
Glutathione peroxidase (G-Px)	Reduces organic hydroperoxides and H_2O_2 to water and the appropriate alcohols	Increased activity	Maintains redox balance by preventing peroxide accumulation	$2\ GSH + H_2O_2 \rightarrow GSSG + 2H_2O$	82
Glutathione (GSH)	Directly scavenges ROS and regenerates other antioxidants	Fluctuates increased synthesis/recycling	Neutralizes ROS and regenerates other antioxidants	$GSH + R^{\bullet} \rightarrow GS^{\bullet} + RH$	83
Vitamin-C (ascorbic acid)	Antioxidant that scavenges free radicals	Utilized to mitigate oxidative damage	Directly neutralizes ROS in the cellular aqueous phase	$C_6H_8O_6 + ROO^{\bullet} \rightarrow C_6H_7O_6^{\bullet} + ROOH$	84
Vitamin-E (tocopherol)	Protects cell membranes from lipid peroxidation	Increased demand	Prevents oxidative damage in cellular membranes, and neutralization of lipid hydroperoxyl radicals	$Tocopherol + ROO^{\bullet} \rightarrow$ tocopherol radical + ROOH	84
Heat shock proteins (HSPs)	ROS scavenging, assist in protein folding, refolding of misfolding peptide repair, and excessive apoptosis	Upregulated in response to oxidative stress	Maintenance of homeostasis and redox balance in cells and tissues under stress conditions induced by CNDs	N/A	85

human non-small cell lung cancer.[69] In another study by Ning *et al.*, he formulated Re-CNDs by herbal extraction for anti-renal cell carcinoma. The CNDs could induce ROS production and mitochondrial dysfunction, further accelerating the release of intracellular calcium ions. The results suggested that Re CNDs could downregulate the abnormally activated PI3K/AKT signaling

pathway and perform the cell cycle, further inhibiting cell proliferation. The prepared Re-CNDs have the potential for the treatment of kidney cancer with high-safety.[70] Therefore, we can control cell apoptosis or cell survival by targeting these signaling pathways. Further research is needed to understand the long-term effects, safety, and efficiency of CNDs in redox biology (Table 3).

5.4. Antioxidant defenses and responses to CND-induced oxidative stress

Incomplete oxygen molecule reduction during aerobic respiration and substrate oxidation produces reactive oxygen species (ROS), which are dealt with by antioxidant defense mechanisms in aerobic organisms. O_2, H_2O_2, and H_2O are produced as oxygen through a series of univalent reductions during cellular metabolism.[66] Examples of potential enzymatic producers of ROS include nitric oxide synthase (NOS), lipoxygenase, xanthine oxidase, cytochrome p450 monooxygenases, components of the mitochondrial electron transport chain, and NADPH oxidase.[77]

Superoxide anion is converted into H_2O_2 with the help of SOD, which is then converted to H_2O by glutathione peroxidases (G-Px), peroxiredoxins (Prxs), or catalase (CAT)[66] (Fig. 5 below). Many biochemical activities, such as defense against pathogens, intracellular signaling, and cell function, depend on low amounts of extracellular or intracellular ROS (*e.g.*, superoxide and H_2O_2).[78] On the other hand, oxidative stress, which has been linked to numerous cardiovascular illnesses, such as hypercholesterolemia, atherosclerosis, hypertension, diabetes, and heart failure, is brought on by high doses and insufficient elimination of ROS, particularly superoxide anion (O_2^-). As a part of the innate immune system, ROS also plays a role in the respiratory burst of neutrophils and the chemotaxis of inflammatory cells into areas of inflammation (Table 4).[79]

6. Immunomodulatory effects of CNDs

CNDs are synthesized from carbon and its derivatives by surface passivation with PEG, PVA, and ALG (alginate). Carbon-based materials have been extensively researched for biological applications because of their special surface characteristics. Zero-dimensional and small sizes among these materials have enormous potential as drug candidates, drug delivery vehicles, functionalization agents, and implant scaffolds.[86]

PEG, ALG, and PVA surface passivating agents are among the most prevalent polymers used in biomedical approaches. PEG has been used in the targeted administration of drugs, and it is commonly recognized that the immune system produces an anti-PEG action. The impact of PEG and PEG-based materials on macrophages has not been investigated at the level of the inflammatory response, despite research using these materials to avoid immune system cell assaults or to produce an anti-inflammatory response.[87]

PVA, on the other hand, has a reputation for not eliciting an immunological reaction. Its bio- and immune compatibility has made it a preferred option for implants. Its removal from the body and absorption by macrophages are two main issues. Alginate is a biomolecule derived from algae that is widely recognized for its ability to stimulate the immune system.[88]

The number of surface-active groups, particularly carboxyl, alkyl, and sp^2-carbon domains (C=C) and C=O groups, was found to affect the UV-induced H_2O_2 scavenging activity of PEG, PVA, and alginate-passivated CNDs. This work treated carbon molasses with various passivation agents, including ALG, PVA, and PEG, to create surface-functionalized carbon nanodots. These CDs were tested for both delivery and immunomodulatory effects.[89]

In summary, the surface passivation of CNDs with different agents like PEG, PVA, and ALG influences their interaction with immune cells, affecting their function and activation.

6.1. Impact of CNDs on immune cell function and activation

There are two types of immunity: innate and adaptive. The innate immune system serves as the first line of defense, employing phagocytic cells, including mast cells, dendritic cells, neutrophils, and macrophages, to react swiftly and broadly to foreign particles.

T and B cells are two examples of specialized cells used by the adaptive immune system to deliver a more focused response. Phagocytic and antigen-presenting cells (APCs) eliminate some antigens, like bacteria and fungi. Among T cells, helper T cells (Th) are divided into subtypes, including Th1, Th2, Th17, Tregs, and Th22. Th1 cells promote inflammation by secreting cytokines such as IFN-γ, IL-2, and TNF-α/β, while Th2 cells mediate anti-inflammatory responses, often counteracting Th1 responses.

Innate and adaptive immune systems are linked with dendritic cells (DCs), helping stimulate or suppress immune responses. Lymphocytes like Natural Killer (NK), T, and B cells fight against pathogens and tumor cells. In cancer, cytotoxic T and NK cells kill tumor cells using cytokines and inhibitors like CTLA-4 and PD-1/PD-L1. However, excessive immune activation can cause chronic inflammation, autoimmunity, and allergic reactions.[90]

Immune cells, including T-cells, dendritic cells, and macrophages, can all have their function altered by CNDs. Encouraging the synthesis of cytokines and chemokines, which are essential for immunological signaling and coordination, can improve the immune response. For instance, CNDs can induce the production of pro-inflammatory cytokines by macrophages, which can strengthen anti-tumor immunity and support the immune system's fight against infections.[91]

Additionally, CNDs can affect the antigen-presenting capabilities of dendritic cells, thus influencing the activation of T cells and subsequent adaptive immune responses. However, the effects of CNDs are highly dependent on their physicochemical properties, such as surface charge, size, and functionalization, which can lead to immune system activation or suppression. These findings highlight the potential of CNDs in biomedical applications, such as vaccine adjuvants and immunotherapies, but also underline the importance of carefully assessing their biocompatibility and immune interactions to avoid unintended immunotoxicity.

6.2. Modulation of inflammatory responses by CNDs

Macrophages play a significant role in disease intermediate states by distinguishing into pro-inflammatory and anti-

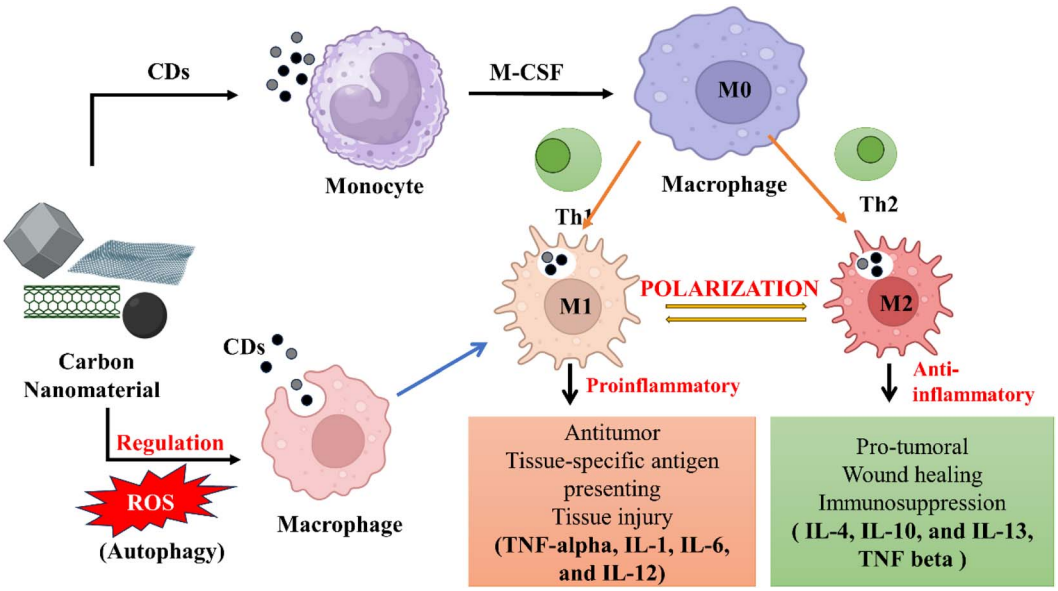

Fig. 6 Monocyte differentiation and macrophage polarization in response to various stimuli. The macrophage polarization process is depicted in the graphic. Monocytes can differentiate into activated M0 macrophages by using macrophage colony-stimulating factor (M-CSF). Then, M0 macrophages may polarize into M1 macrophages in response to lipopolysaccharide (LPS) or Th1 cytokines such as interferon-γ (INF-γ) and tumor necrosis factor-α (TNF-α). Alternatively, M0 macrophages may polarize into M2 macrophages in response to Th2 cytokines, such as interleukin-13 (IL-13) and interleukin-4 (IL-4).

inflammatory states, secreting cytokines. Their role is briefly explained in Fig. 6. Phagocytic activity is one of the most crucial roles that macrophages play. It is an endocytosis characterized by the engulfment of extracellular particles by a cell membrane, which permits their entry into the cell's cytoplasm. Macrophages are important members of the immune system that consume a wide range of particles, such as bacteria, altered lipids, and even whole dead cells.[92] Because of their phagocytic function and other functions in immune responses, macrophages are frequently used as targets in therapeutic trials. Despite their widespread use, little research has been performed to examine how CNDs affect primary macrophages' capacity for phagocytic activity.

M1 macrophages secrete pro-inflammatory cytokines such as TNF-alpha, IL-1, IL-6, and IL-12. These cytokines stimulate monocytes in circulation to develop into M1 macrophages and attract other immune cells. M1 macrophages are identified by receptors such as CD64, CD68, and CD80. While they are important for host defense, their activity can lead to excessive inflammation in the disease state. On the other hand, M2 macrophages release anti-inflammatory cytokines including IL-4, IL-10, and IL-13, to help heal tissue, and remove cellular debris.[93]

6.3. Effects of CNDs on host defense mechanisms and immune regulation

Surface modification methods involve enhancing immune regulation. A common method for the surface modification of CNDs includes covalent functionalization, doping with heteroatoms, passivation, and bioconjugation. These methods enhance the optical properties of CNDs and their interaction with biological systems, which could improve their biocompatibility.[94]

The overall impact of CNDs on immune regulation and host defense mechanisms includes various aspects. Vaccination is essential for enhancing both animal husbandry and public health. Essentially, they train the subject's immune system to produce the right immunity against the infectious pathogen. For vaccination to be successful, adjuvants are essential. They enable the immune system to properly activate against the target antigen. Adjuvants help create strong, long-lasting immune responses against specific antigens and ensure the right type of immune reaction is triggered.

In biomedical applications, nanomaterials are frequently used as carriers to enhance therapy delivery and efficacy. Various nanocarrier systems, such as silica, gold, titanium, graphene oxide nanoparticles, and oil-in-emulsion or polymeric nanovesicles, have been studied for their potential to enhance the bioavailability of treatments by aiding the delivery of adjuvant–antigen complexes.[95,96]

In this study, researchers synthesized aluminum-doped carbon dots (Al-CDs) using a novel thermal synthesis technique with licorice root extract and aluminum chloride ($AlCl_3$). This approach avoided heat-induced deformities by incorporating $AlCl_3$ directly into the CD structure, forming bonds through electrostatic interactions. These Al-CDs induce immunostimulatory activity compared to conventional aluminum salt. When aluminum ions are incorporated into CDs' carbon nanostructure, macrophages' toll-like receptors can recognize them, which increases the CDs' ability to stimulate the production of TNF-α and IL-1β cytokines. When aluminum is added to CDs, more oxygen-containing functional groups are present, increasing the negative surface charge and particle size. These changes may produce better adjuvant qualities *in vitro* than aluminum salts. Although Al-CDs have a stronger adjuvant effect on macrophages than pure

aluminum salts, this discovery clarifies that Al-CDs can achieve effective adjuvant action with a significantly reduced aluminum level, potentially lowering the negative effects linked to typical adjuvants' greater aluminum content.[89] Inflammatory responses occur in tissues due to danger signals from infections, tumors, or, in autoimmune diseases, the body's antigens. Immunomodulatory agents that can positively modify immune reactions could be used as adjuvants in vaccines or as immune system boosters for those with immunodeficiencies. Conversely, anti-inflammatory agents could help manage inflammation in autoimmune and inflammatory diseases.[97]

In this study, macrophages secrete pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β when activated and are important players in the immune response. This study focused on the *in vitro* effects of Al-doped CDs (Al-CDs) on mammalian macrophages. The findings suggest that Al-CDs have superior adjuvant potential compared to traditional aluminum salts, marking the first report of this kind.[98]

In summary, the immunomodulatory effects of CNDs are multifaceted, influencing immune cell function, inflammatory responses, and overall immune regulation. Understanding these effects is crucial for developing CND-based therapeutic strategies for various diseases.

Numerous studies have investigated the cytotoxicity of CDs utilizing various mammalian cell lines and variations in CD composition and surface functionalization. Since they are considered inherently non-cytotoxic, they can be used in various biomedical applications. However, most cytotoxicity studies have been conducted in the dark to date. Numerous suggested CD uses include light (*e.g.*, photovoltaic cells, light-emitting diodes, bioimaging, and photocatalysis). Additionally, CDs are photoactive; according to current research, when exposed to light, they generate reactive oxygen species, which are harmful to bacteria and yeast. Even though CDs are photoactive, it is still unclear if they break down when exposed to light and whether this photodegradation harms human cells.[99] In summary, the immunomodulatory effects of CNDs are multifaceted, influencing immune cell function, inflammatory responses, and overall immune regulation. Understanding these effects is crucial for developing CND-based therapeutic strategies for various diseases.

7. Biomedical applications of CNDs and their impact on the immune system

7.1. Wound healing

Skin is the largest and most important protective layer and is constantly at risk of injury from burns, cuts, and surgeries. These wounds can easily become infected with bacteria, slowing healing and leading to serious problems. Antibiotics have traditionally been used to fight these infections, but overuse has made some bacteria resistant. To address this issue, scientists are developing new wound dressings made from special materials such as CNDs that can kill bacteria effectively because the CNDs have ROS-generating and scavenging properties. These innovative materials offer a promising alternative to antibiotics for treating wound infections and promoting faster healing.[100]

When neutrophils and macrophages approach a wound site, they naturally create reactive oxygen species (ROS). Non-phagocyte cells that generate ROS, including fibroblasts, can be stimulated by inflammatory cytokines like interleukin-1, PDGF, and EGF. ROS is a crucial component of the healing process since it is a cellular messenger that initiates several molecular and cellular biological processes, such as VEGF production stimulation in keratinocytes by H_2O_2. This demonstrates that oxidants and their derivatives are prevalent at the site of a wound, but their accumulation results in tissue and cell necrosis, which impedes the healing process. Cells utilize two strategies to detoxify and neutralize excess ROS: ROS scavenging enzymes include catalases, SOD, and various peroxidases, as well as small antioxidant molecules such as ascorbate, sugars (mainly mannitol), and polyunsaturated fatty acids. As a result, compounds having antioxidant action may help hasten the healing of wounds.[101]

Four overlapping processes comprise the wound healing process: extracellular matrix remodeling, cell proliferation, inflammation, and homeostasis. The initial action is taken right away following skin damage. Infection at the site of the injury is prevented during the inflammatory stage. Using phagocytosis to remove injured cells and other debris stops the development of germs and speeds up the healing of wounds.[102] Excessive inflammation occurs frequently around the wound, which can cause overproduction of ROS and induce oxidative stress.[103] Zhang *et al.* synthesized Ce-CQDs that combined antioxidant activity and wound healing promotion in Sprague-Dawley rats. These Ce-CQDs generated ROS under UV light to kill microbes, showing excellent hydrophilicity, biocompatibility, photoluminescence properties, and photostability. Ce-CNDs exhibit certain antibacterial capabilities under UV radiation because they have good PL properties.[104]

Lee *et al.* designed a CD-embedded hyaluronic acid hydrogel (CD-gel) for photodynamic bacterial eradication. This gel releases CQDs in response to microbial hyaluronidase, generating singlet oxygen under light to kill bacteria. *In vitro* tests showed 99% and 97% efficiency against *S. aureus* and *Escherichia coli* (*E. coli*), respectively, and *in vivo* tests showed accelerated wound healing.[105]

These studies demonstrate how CNDs can fight bacterial infections and speed up wound healing without causing antibiotic resistance.

7.2. Anti-inflammatory effect

As the body's natural defensive mechanism, inflammation is an old biological process that promotes health in humans.[106] The body's first line of defense, inflammation, may activate both immunological and non-immune cells, such as neutrophils, macrophages, monocytes, mast cells, and lymphocytes, as well as fibroblasts and vascular endothelial cells. These cells promote the regeneration and repair of injured tissue, which restores cellular homeostasis and protects the host against pathogens, infections, and toxins.[107]

Acute inflammation is usually localized and less severe; chronic inflammation can develop if acute inflammation is helpless to eliminate a pathogen. Chronic inflammation can develop into an autoimmune condition when ROS builds up. ROS assaults healthy host cells, resulting in disease and the loss of cellular homeostasis. Lifestyle factors that can cause inflammation include drinking alcohol, being exposed to radiation, stress, and smoking cigarettes. These factors can also cause ROS to be produced.[107]

ROS can modulate a wide range of inflammatory markers, including chemokines, cytokines, cyclooxygenase-2 (COX-2), and proinflammatory transcription factors, such as tumor necrosis factor (TNF), nuclear factor kappa light chain enhancer of activated B-cells (NF-κB), p53, nuclear factor erythroid 2-related factor 2 (Nrf2), activator protein 1 (AP-1), hypoxia-inducible factor 1α (HIF-1α), peroxisome proliferator-activated receptor γ (PPAR-γ), and β-catenin/Wnt.[108]

Some researchers synthesized various CQDs that help with anti-inflammatory and antimicrobial effects. Das *et al.* created green chili extract-derived CQDs *via* microwave irradiation. These CQDs act as redox buffers, reducing oxidative stress and inflammation while supporting long-term cell tracking. Wang *et al.* prepared CQDs from citric acid and glutathione using a hydrothermal approach. These CQDs scavenged ROS, protecting macrophages from LPS-induced inflammation, reducing intracellular ROS by 98%, and suppressing NF-κB signaling and IL-12 expression.[109]

7.3. Anti-tumor therapy

Cancer, which is characterized by the uncontrolled growth of malignant cells, continues to be a major global health problem due to its high rates of morbidity and mortality, even with breakthroughs in therapy. Early detection and intervention are key to lowering costs and improving patient survival. Solid tumors may be diagnosed *via* biopsies and imaging procedures, including CT, SPECT, PET, MRI, and B-mode ultrasound.[110] PTT is a promising cancer treatment that uses absorbed light energy to generate heat, which kills cancer cells. This method is favored for its precise control, low toxicity, and quick response.[111] Some researchers developed CNDs for various types of antitumor therapy which are mentioned below:

Li *et al.* evaluated dopamine carbon dots (DA-CDs) as photothermal therapy (PTT) agents for cancer treatment. They demonstrated high photothermal conversion efficiency and effective cancer cell killing in HeLa cells under 808 nm irradiation, suggesting DA-CDs as promising PTT agents for cancer therapy.[112] More research is necessary to enable CNDs to be delivered to the nuclei that target damaged genetic material, which boosts antitumor effectiveness. These are more vulnerable to the effects of oxidative stress because cancer cells often create larger quantities of ROS than normal cells. This sensitivity can be exploited for cancer therapies that increase intratumoral ROS concentrations. CQDs have shown promise in enhancing PDT effects and in ROS scavenging strategies.[58]

Here are some notable examples: polythiophene-based S-CQDs were created by Li *et al.* to treat oral squamous cell cancer. These S-CQDs produced more singlet oxygen (O_2) under light irradiation, and exhibited greater anti-tumor activity than the conventional photosensitizer 5-aminolevulinic acid (ALA). This was because the singlet oxygen generation was higher, inducing acute stress, Ca^{2+} influx, overexpression of Bax and caspase-3, and downregulation of Bcl-2.[113] High ROS in tumor cells and the tumor microenvironment (TME) can stimulate immune-suppressive cells, block immune cell activity, and encourage cancer-causing mutations.[79] Within the TME, antioxidant therapies might lessen immunological suppression, DNA damage, and cell survival and proliferation.[113] Ardekani *et al.* created N-doped carbon nanohybrid dots (DOX-loaded CND-P) loaded with doxorubicin (DOX) for killing MCF-7 cancer cells. The combined photothermal and chemotherapeutic effects of CND-P and DOX enhanced cell apoptosis.[114] A gold/gadolinium-doped carbon dot (Au/Gd CDs) nanocomposite was created by Gedda *et al.* for MRI and photothermal treatment (PTT). With its paramagnetic characteristics, photostability, and near-infrared (NIR) absorbance, this nanocomposite efficiently targeted tumor cells and offered superior MRI imaging capabilities.[115]

PDT creates ROS to treat cancer by using photosensitizers and visible light.[116] High singlet oxygen yields, nontoxicity in the dark, water solubility, photostability, and the capacity to absorb light within the therapeutic window are all desirable qualities in PDT drugs. CDs are attractive PDT agents because of their strong water dispersibility, low toxicity, great biocompatibility, and photostability.[117] Ge *et al.* developed a PDT agent using polythiophene-derived GQDs with a high singlet oxygen yield of 1.3, double that of other agents. *In vitro* studies showed that GQDs effectively shrank HeLa cells upon irradiation. *In vivo* studies in mice demonstrated GQDs' potential as highly efficient PDT agents for cancer therapy, surpassing conventional reagents.[118] Yao *et al.* created HFn (DOX)/CDs nanoparticles for combined chemo-photodynamic therapy. These nanoparticles use heavy-chain ferritin (HFn) to carry carbon dots (CDs) and doxorubicin (DOX), targeting MCF-7 cancer cells. DOX damages DNA, and CDs generate reactive oxygen species (ROS) under laser light, contributing to cell damage. In studies with mice, the nanoparticles showed greater effectiveness in inhibiting tumor growth and were less toxic to normal tissues compared to DOX alone.[119] These studies illustrate how CQDs can be used to either enhance ROS levels for cancer cell destruction or to scavenge ROS to protect cells, showing the versatility of CQDs in cancer therapy.

7.4. Antiviral therapy

Nanoparticles (NPs) in nanotechnology offer significant potential in fighting viruses like coronaviruses. Due to their small size, large surface area, and tuneable surface charge, NPs effectively penetrate tissues, deliver drugs, and enhance antiviral action. These properties make them promising tools for treating viral diseases and cancers.[120] The encapsulation, surface functionalization, and structural changes of nanoparticles can optimize the delivery of drugs to certain tissues or

cellular areas. Using polymer nanoparticles, liposomes, dendrimers, nano-emulsions, and nanosuspensions as nanotechnology platforms for RNA virus diagnostics is possible. Even though these nanomaterials have made advancements against viral threats, they still require improvements in patient adherence, water solubility, biostability, and bioavailability.[121]

CDs have shown strong antiviral activity due to their properties and affinity for specific cellular sites. For example, the two lipid layers that make up the outer shell of HIV include several protein spikes, such as the glycoproteins gp120 and gp41. The interaction between T cell CD4 receptors and gp120 causes HIV to attach to T cells. CDs can bind to HIV because they attract the spike proteins of gp120 receptors when they have certain surface functional moieties. As a result, using CDs will prevent viruses from entering host cells.[122]

Theoretically, viruses enter host cells by endocytosis and multiply quickly inside them. Carbon dots (CDs) target viral spike proteins and host cell receptors to block viral entry and replication. CDs can interfere with various stages of infection, including attachment, penetration, replication, and budding. Recent research has demonstrated that due to their biocompatibility, CDs produced from biogenic sources such as curcumin, glycyrrhizin, *etc.*, are more promising and enhance both *in vitro* and *in vivo* effectiveness. Recently, some studies have demonstrated that certain carbon quantum dots have high antiviral activity against coronavirus, norovirus, and herpesvirus. CQDs are derived from the benzoxazine monomer and are reported as broad-spectrum agents that block viral activity against Japanese encephalitis, Zika, and dengue viruses and non-enveloped virus-like parvovirus.[123] The primary step in viral infection is the attachment of the virus to the host cell. By preventing this attachment, we can effectively inactivate the virus. For instance, in HIV infections, the virus's gp120 protein binds to the CD4 receptor and co-receptors (CCR5 or CXCR4) on T cells. Inhibiting this binding can block the entry of the virus into the host cell. Some studies demonstrated examples:

Fahmi and colleagues have utilized CDs as inhibitors of viral entry. Their approach involves using CDs to prevent the gp120 protein of HIV from binding to the CD4 receptor or co-receptor CCR5 on the host cells, thereby obstructing the viral entry process.[124]

Currently, there are some existing conventional antiviral agents or drugs that still have many limitations, such as drug resistance, a side effect due to toxicity, and high cost. Still, there are advanced nanomaterials capable of penetrating cells and inhibiting viral replication, acting as drug carriers, and certain drugs with antiviral properties. Some nanoparticles can attack and kill viruses *via* photothermal and photocatalysis-induced ROS.[125] In addition, CQDs can target and bind to viruses and attach to the surface of the cell membrane to prevent virus–cell interaction. Boronic acid-modified CQDs made by the hydrothermal technique were effective against herpes simplex virus type 1 (HSV-1) infection in a prior study conducted by Barras *et al.*[126] In this study, we demonstrated that CQDs had stronger antiviral effects when compared to other known antiviral nanoparticle-based inhibitors (such as poly-L-lysine, dextran sulfate, and Ag nanoparticles treated with tannic acid).

7.5. Drug delivery and bioimaging

CNDs are highly suitable for *in vivo* drug delivery and have excellent bioimaging properties due to their excellent biocompatibility and efficient clearance. They can be functionalized with various groups (amino, carboxyl, and hydroxyl) to carry therapeutic agents, making them ideal for theragnostic nanomedicines. Drug delivery can be tracked in real-time because of their fluorescence properties. The diagnosis and treatment are greatly aided by bioimaging and gene therapy. Multifunctional CDs, including hyaluronic acid-linked CDs, transferrin, RGD peptides, and folic acid (FA), have been used as fluorescent probes for rapid tumor detection and targeted therapy in recent years.[126] According to Zhang *et al.*, photostable FA-CDs coupled with green fluorescent CDs enter HepG2 specifically by endocytosis mediated by the folate receptor (FR). In diverse combinations, the FA-CDs identified FR-positive cancer cells.[127] Due to the CNDs' fluorescence properties, release at the tumor site can be monitored.[1]

In this area, the delivery of genetic materials or silencing nucleic acid (SiRNA) into cells affects gene therapy-specific targets and signaling pathways, which indicates or reverses the disease's progression. Gene therapy's fundamental idea is to transfer genetic material to a patient's cell nucleus *via* RNA transfection to express a target gene or make a protein.[128] Gene therapy is a viable treatment option for conditions like cancer, Parkinson's disease, AIDS, and cardiovascular diseases. Gene carriers are divided into viral and non-viral vectors. Because non-viral vectors lack anterograde and retrograde transportation, they are more difficult to disperse in the targeted tissue.[116]

Ray *et al.* created water-soluble blue and yellow fluorescent CDs inserted into HepG2 cells for bioimaging in the first investigation using carbon soot and nitric acid. TTDDA (4,7,10-trioxa-1,13-tridecanediamine) passivated CDs were utilized by Qiao *et al.* to image COS-7 cells.[115] Wang *et al.* used pyrolysis to generate biocompatible CDs and silica nanoparticles (12 nm) that were then used for BGC823 cell bioimaging.[129] Cao *et al.* used fluorescent CDs for cellular imaging for the first time. The authors employed two-photon luminescence microscopy in human breast cancer (MCF-7 cells) using PPEI-EI passivated CDs.[17] Yang *et al.* labeled HepG2 cells with green fluorescent CDs made from glucose and utilized DAPI counterstaining to examine their intracellular location, which revealed cytoplasmic localization surrounding the nucleus.[130] Peng *et al.* prepared water-soluble fluorescent CDs from carbon fibers for bioimaging breast T47D cancer cells.[131] Tao *et al.* used yellow fluorescent CDs derived from carbon nanotubes and graphite for *in vivo* bioimaging and labeling. CDs were injected into a nude mouse, showing accumulation in the liver and spleen and later in the kidney, indicating urinary clearance.[132] Zhang *et al.* synthesized yellow fluorescent CDs (5–10 nm) from graphite rods using an electrochemical method, followed by reduction with hydrazine. These CDs were used for bioimaging human lung A549 and breast MCF-7 carcinoma cells.[133]

7.6. Antimicrobial therapy

Antibiotics have been a major weapon in the fight against infectious diseases, but the complexity and expense of drug

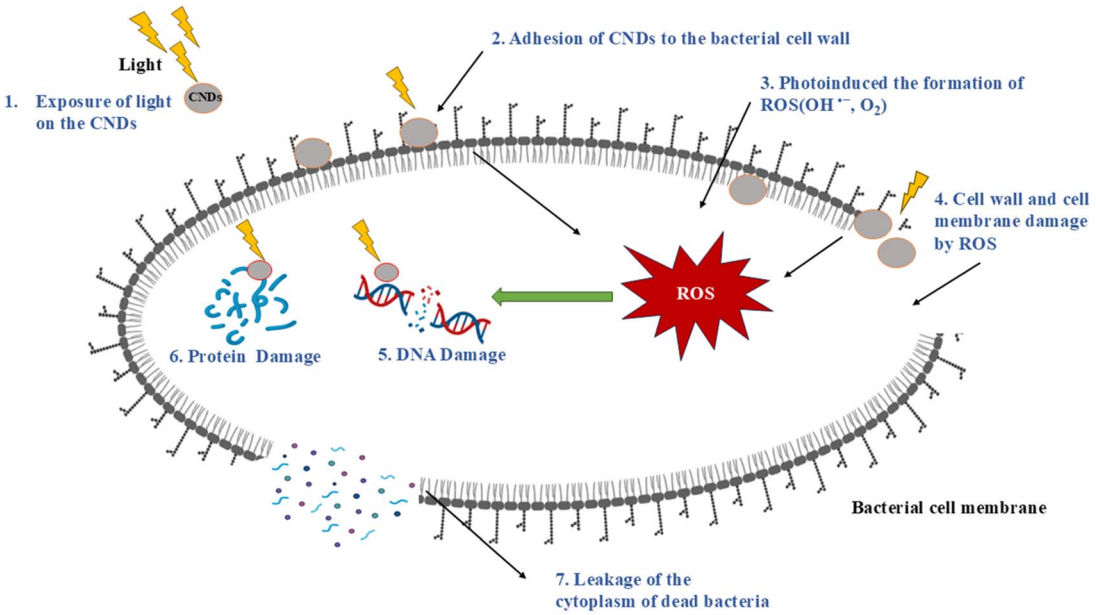

Fig. 7 Antibacterial therapy of CNDs. Light can be absorbed by CNDs at wavelengths ranging from near UV to visible to near-IR. These comprise ROS produced during photoinduction, CND adhesion to bacterial surfaces, and ROS interacting with bacterial cells in visible light. Bacterial cell membrane damage, changes in the morphological modifications of the cell membrane, -induced DNA/RNA damage, expressions of significant genes that inhibit, and the induction of oxidative damage in proteins are among the events that can occur. Due to the generation of singlet oxygen (O_2) or hydroxyl free radicals (OH•), it damages some important biomolecules in the cell and causes cytoplasmic leakage, which results in cell death.

research, clinical testing, and regulatory processes mean that developing next-generation antibiotics will take a while. Furthermore, bacteria possess an array of mechanisms that enable them to develop resistance.[134] Bacterial infections can worsen health and delay wound healing for patients with other conditions, such as cancer. Current disinfection methods, such as chemical sprays, UV light, and silver nanoparticles, have significant drawbacks, like being harmful to people and hard to control. Therefore, there is a need for better sterilization techniques to reduce infection risks effectively. So we use an alternative known as antibacterial photodynamic therapy (APDT).[135]

Researchers agree that CNDs are nontoxic in *in vitro* and *in vivo* settings.

CNDs inhibit the growth of bacteria or kill them, which causes the cytoplasm to leak through various complex processes, including ROS generation, disruption of the cell wall, fragmentation, and condensation of genetic material DNA. According to recent research findings, the primary mechanism of CNDs' antibacterial activity is communicated through the generation of ROS.[136] Light-activated bacterial eradication is among the most effective and secure methods (Fig. 7).

ROS are infamous substances or atoms that are known to induce mitochondrial dysfunction, lipid peroxidation, intracellular irreversible protein inactivation, and progressive deterioration of the cell membrane that eventually result in necrosis/apoptosis and cell death.[137] CNDs represent a novel class of effective antibacterial agents easily triggered by visible or ambient light. However, a thorough comprehension of the mechanisms behind the production of ROS by various CNDs and the consequent antibacterial activity is still lacking.

On the other hand, in some reported studies, Kováčová *et al.* synthesized hydrophobic CDs and embedded them in polyurethane and polydimethylsiloxane matrices to create polymeric composites. These composites were tested for antibacterial properties and demonstrated significant activity against *S. aureus*, *Escherichia coli* (*E. coli*), and pneumonia. The composites generated singlet oxygen upon blue light irradiation, resulting in up to 5 log reductions in bacterial populations after 60 min of exposure.[138]

Yan *et al.* used hydrothermal techniques to produce CNDs coated with TiO_2 compared to pure TiO_2, and these composites showed increased antibacterial activity against *S. aureus* and *E. coli*. Better dispersibility, strong visible light absorption, and higher ROS formation under visible light irradiation were cited for improved performance.[139]

8. Conclusion

This review examined the recent breakthroughs in carbon nanodot research and their potential utility in treating diseases. Furthermore, they have outstanding luminescence, remarkable biocompatibility, low photobleaching, high photostability, high quantum yields, low toxicity, greater potential for surface functionalization and doping, extensive chemical stability, and many other remarkable optical and physical properties. These characteristics are used in biomedical applications, including biosensing, bioimaging, drug and gene delivery, antioxidant, antibacterial, and antimicrobial therapy, cancer detection, and treatment. They also play a part in treating neurodegenerative diseases like Parkinson's and Alzheimer's. We have also

explored the latest research advancements related to carbon nanodots, covering their various types, synthesis methods, physicochemical properties, and applications.

Despite promising results, further investigation into their toxicity profiles and biodegradation mechanisms is needed to ensure their safe and effective use in drug delivery. They also face challenges as carriers for phototherapy agents, particularly in improving loading efficiency, stability, and tumor targeting during circulation to prevent systemic toxicity. Regulating the excitation state and inactivation pathways of CNDs with photodynamic and photothermal properties is essential for their successful application in phototherapy.

9. Future prospectives

CNDs are attracting significant attention in nanoscience due to their unique optoelectronic properties, photostability, and biocompatibility. Their surface carboxyl groups enhance water solubility and compatibility with biological systems. However, before CDs can be widely used in clinical applications, challenges such as toxicity, body clearance, synthesis scalability, and environmental impact need to be addressed. Efforts should focus on making CNDs non-toxic, biocompatible, and customizable for various biomedical applications. Improved fluorescent materials with better optical and biological properties are needed for live cell imaging, and overcoming the blood–brain barrier (BBB) for drug delivery remains a major challenge. CNDs have potential as temperature and pH sensors due to their fluorescence response to these factors, making them suitable for cellular temperature sensing. Even though their therapeutic and diagnostic uses seem promising, further study is necessary to fully comprehend their processes and advance their commercialization and clinical application. Further investigation on CDs might lead to significant progress in the field of biological applications in the future.

Data availability

Our article is a review article, so all the results reported are cited from the literature review and those are properly mentioned in text and reference sections. No primary research results, software, or code have been included, and no new data were generated or analyzed as part of this review. The figures are self-prepared and for illustration purposes only and do not include any scientific results such as spectroscopic/microscopy images/plots/graphs for qualitative or quantitative interpretation.

Author contributions

Surabhi Verma: formal analysis, investigation, conceptualization, writing – original draft; Manini Bhatt: writing – review, conceptualization, and editing; Dr Bodhisatwa Das: conceptualization, funding acquisition, project administration, supervision, writing – review and editing.

Conflicts of interest

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

Abbreviations

CD	Carbon dots
CNDs	Carbon nanodots
RTP	Room temperature phosphorescence
PL	Photoluminescence
CQDs	Carbon quantum dots
GQDs	Graphene quantum dots
ERKs	Extracellular signal-regulated kinases
JNKs	c-Jun N-terminal kinases
BBB	Blood–brain barrier
PDT	Photodynamic therapy
PTT	Photothermal therapy
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
APDT	Antibacterial photodynamic therapy
DA-CDs	Dopamine carbon dots
TNF	Tumor necrosis factor
HIF-1α	Hypoxia-inducible factor 1α
COX-2	Cyclooxygenase-2
NF-κB	Nuclear factor kappa light chain enhancer of activated B-cells
PPAR-γ	Peroxisome proliferator-activated receptor γ
IL-6	Interleukin-6
H_2O_2	Hydrogen peroxide
APCs	Antigen-presenting cells
HSPs	Heat shock proteins
CAT	Catalase
SOD	Superoxide dismutase
HAT	Hydrogen atom transfer
DPPH	2,2-Diphenyl-1-picrylhydrazyl radical
CNF	Carbon family of nanomaterials
G-Px	Glutathione peroxidases
Prxs	Peroxiredoxins
GSH	Glutathione
FA-CDs	Folic acid carbon dots
FR	Folate receptor

References

1 J. A. Jaleel and K. Pramod, *J. Control. Release*, 2018, **269**, 302–321.
2 H. Huang, H. Ge, Z. Ren, Z. Huang, M. Xu and X. Wang, *Front. Bioeng. Biotechnol.*, 2021, **9**, 617097.

3 A. Ghosh, U. Basu, M. Bhatt, T. K. Ghosh and B. Das, Carbon Quantum Dots, a Novel Theranostics Nanoprobe in Biomedical Engineering, *Nanomedicine in Translational Research*, ed. C. P. Sharma and K. Kaladhar, Academic Press, 2025, pp. 165–187.
4 L. Lin, Y. Luo, P. Tsai, J. Wang and X. Chen, *TrAC, Trends Anal. Chem.*, 2018, **103**, 87–101.
5 D. Cammi, K. Zimmermann, R. Gorny, A. Vogt, F. Dissinger, A. Gad, N. Markiewcz, A. Waag, J. D. Prades, C. Ronning, S. R. Waldvogel and T. Voss, *J. Phys. Chem. C*, 2018, **122**, 1852–1859.
6 X. Zhai, P. Zhang, C. Liu, T. Bai, W. Li, L. Dai and W. Liu, *Chem. Commun.*, 2012, **48**, 7955–7957.
7 W. Zhang, Z. Zeng and J. Wei, *J. Phys. Chem. C*, 2017, **121**, 18635–18642.
8 D. R. d. S. Souza, J. P. de Mesquita, R. M. Lago, L. D. Caminhas and F. V. Pereira, *Ind. Crops Prod.*, 2016, **93**, 121–128.
9 Y. Qiu, Z. Wang, A. C. E. Owens, I. Kulaots, Y. Chen, A. B. Kane and R. H. Hurt, *Nanoscale*, 2014, **6**, 11744–11755.
10 U. Agbogo, B. Rifore, C. Arum, P. Iorver, S. Tanko and M. Joshua, *FUDMA J. Sci.*, 2024, 93–102.
11 L. Cui, X. Ren, M. Sun, H. Liu and L. Xia, *Nanomaterials*, 2021, **11**, 3419.
12 H. J. Yoo, B. E. Kwak and D. H. Kim, *Carbon*, 2021, **183**, 560–570.
13 J. Liu, R. Li and B. Yang, *ACS Cent. Sci.*, 2020, **6**, 2179–2195.
14 X. Xu, R. Ray, Y. Gu, H. J. Ploehn, L. Gearheart, K. Raker and W. A. Scrivens, *J. Am. Chem. Soc.*, 2004, **126**(40), 12736–12737.
15 O. Mkhari, T. D. Ntuli, N. J. Coville, E. N. Nxumalo and M. S. Maubane-Nkadimeng, *J. Lumin.*, 2023, **255**, 119552.
16 D. Ozyurt, M. Al Kobaisi, R. K. Hocking and B. Fox, *Carbon Trends*, 2023, **12**, 100276.
17 L. Cao, X. Wang, M. J. Meziani, F. Lu, H. Wang, P. G. Luo, Y. Lin, B. A. Harruff, L. M. Veca, D. Murray, S.-Y. Xie and Y.-P. Sun, *J. Am. Chem. Soc.*, 2007, **129**, 11318–11319.
18 H. Li, Z. Kang, Y. Liu and S. T. Lee, *J. Mater. Chem.*, 2012, **22**, 24230–24253.
19 X. Wang, Y. Feng, P. Dong and J. Huang, *Front. Chem.*, 2019, **7**, 671.
20 X. Michalet, F. F. Pinaud, L. A. Bentolila, J. M. Tsay, S. Doose, J. J. Li, G. Sundaresan, A. M. Wu, S. S. Gambhir and S. Weiss, *Science*, 2005, **307**, 538–544.
21 Z. L. Wu, Z. X. Liu and Y. H. Yuan, *J. Mater. Chem. B*, 2017, **5**, 3794–3809.
22 K. O. Boakye-Yiadom, S. Kesse, Y. Opoku-Damoah, M. S. Filli, M. Aquib, M. M. B. Joelle, M. A. Farooq, R. Mavlyanova, F. Raza, R. Bavi and B. Wang, *Int. J. Pharm.*, 2019, **564**, 308–317.
23 P. K. Yadav, S. Chandra, V. Kumar, D. Kumar and S. H. Hasan, *Catalysts*, 2023, **13**(2), 422.
24 L. Bao, C. Liu, Z.-L. Zhang and D.-W. Pang, *Adv. Mater.*, 2015, **27**, 1663–1667.
25 M. Liu, *Nanoarchitectonics*, 2020, **1**, 1–12.
26 Y. Park, J. Yoo, B. Lim, W. Kwon and S.-W. Rhee, *J. Mater. Chem. A*, 2016, **4**, 11582–11603.
27 R. Atchudan, T. N. J. I. Edison and Y. R. Lee, *J. Colloid Interface Sci.*, 2016, **482**, 8–18.
28 A. Kumar, S. Asu, P. Mukherjee, P. Singh, A. Kumari and S. K. Sahu, *J. Photochem. Photobiol. A Chem.*, 2021, **406**, 113019.
29 J. Guo, W. Lu, H. Zhang, Y. Meng, F. Du, S. Shuang and C. Dong, *Sens. Actuators, B*, 2021, **330**, 129360.
30 X. Yang, X. Yang, Z. Li, S. Li, Y. Han, Y. Chen, X. Bu, C. Su, H. Xu, Y. Jiang and Q. Lin, *J. Colloid Interface Sci.*, 2015, **456**, 1–6.
31 Q. Fu, S. Sun, K. Lu, N. Li and Z. Dong, *Chin. Chem. Lett.*, 2024, **35**, 109136.
32 Q. Xu, P. Pu, J. Zhao, C. Dong, C. Gao, Y. Chen, J. Chen, Y. Liu and H. Zhou, *J. Mater. Chem. A*, 2015, **3**, 542–546.
33 Y. Li, C. Lei, J. Yang, X. Liu and K. Zhang, *Appl. Surf. Sci.*, 2022, **606**, 154939.
34 S. Samatya Ölmez, A. Balbay and C. Saka, *Int. J. Hydrogen Energy*, 2022, **47**, 31647–31655.
35 Z. T. Rosenkrans, T. Sun, D. Jiang, W. Chen, T. E. Barnhart, Z. Zhang, C. A. Ferreira, X. Wang, J. W. Engle, P. Huang and W. Cai, *Adv. Sci.*, 2020, **7**, 2000420.
36 D. Xing, A. Koubaa, Y. Tao, S. Magdouli, P. Li, H. Bouafif and J. Zhang, *Polymers*, 2022, **15**, 136.
37 Q. Xu, W. Cai, M. Zhang, R. Su, Y. Ye, Y. Li, L. Zhang, Y. Guo, Z. Yu, S. Li, X. Lin, Y. Chen, Y. Luo, J. Street and M. Xu, *RSC Adv.*, 2018, **8**, 17254–17262.
38 Y.-F. Wu, H.-C. Wu, C.-H. Kuan, C.-J. Lin, L.-W. Wang, C.-W. Chang and T.-W. Wang, *Sci. Rep.*, 2016, **6**, 21170.
39 D. Zhao, X. Liu, R. Zhang, X. Xiao and J. Li, *J. Inorg. Biochem.*, 2021, **214**, 111306.
40 X.-Y. Zhang, Y. Li, Y.-Y. Wang, X.-Y. Liu, F.-L. Jiang, Y. Liu and P. Jiang, *J. Colloid Interface Sci.*, 2022, **611**, 255–264.
41 B. Shi, Y. Su, L. Zhang, M. Huang, R. Liu and S. Zhao, *ACS Appl. Mater. Interfaces*, 2016, **8**, 10717–10725.
42 V. Arul, P. Chandrasekaran, G. Sivaraman and M. G. Sethuraman, *Diamond Relat. Mater.*, 2021, **116**, 108437.
43 G. Redondo-Fernandez, J. Cigales Canga, A. Soldado, J. Ruiz Encinar and J. M. Costa-Fernandez, *Anal. Chim. Acta*, 2023, **1284**, 341874.
44 S. Ching, J. Tai, J. Khor, J. L. Wong, J. Lee, K. Leong, S. Pichiah and A. Abd Aziz, *Perovskite Oxide–Based Photocatalysts for Excellent Visible Light–Driven Photocatalysis and Energy Conversion*, 2019, pp. 1–33.
45 S. B. Mayegowda, G. Sarma, M. Gadilingappa, S. Alghamdi, A. Aslam, B. Refaat, M. Almehmadi, M. Allahyani, A. Alsaiari, A. Aljuaid and I. Al-Moraya, *Green Process. Synth.*, 2023, **12**(1), DOI: **10.1515/gps-2023-0001**.
46 H. Kaurav, D. Verma, A. Bansal, D. N. Kapoor and S. Sheth, *Front. Chem.*, 2023, **11**, 1227843.
47 B. Chen, F. Li, S. Li, W. Weng, H. Guo, T. Guo, X. Zhang, Y. Chen, T. Huang, X. Hong, S. You, Y. Lin, K. Zeng and S. Chen, *Nanoscale*, 2013, **5**, 1967–1971.
48 L. Wang, X. Wang, A. Bhirde, J. Cao, Y. Zeng, X. Huang, Y. Sun, G. Liu and X. Chen, *Adv. Healthc. Mater.*, 2014, **3**, 1203–1209.

49 S. Y. Park, H. U. Lee, E. S. Park, S. C. Lee, J.-W. Lee, S. W. Jeong, C. H. Kim, Y.-C. Lee, Y. S. Huh and J. Lee, *ACS Appl. Mater. Interfaces*, 2014, **6**, 3365–3370.
50 Q. Wang, X. Liu, L. Zhang and Y. Lv, *Analyst*, 2012, **137**, 5392–5397.
51 V. N. Mehta, S. Jha and S. K. Kailasa, *Mater. Sci. Eng. C*, 2014, **38**, 20–27.
52 M. Otten, M. Hildebrandt, R. Kühnemuth and M. Karg, *Langmuir*, 2022, **38**, 6148–6157.
53 L. Yan, Y. Yang, C.-Q. Ma, X. Liu, H. Wang and B. Xu, *Carbon*, 2016, **109**, 598–607.
54 M. He, M. Wang, T. Xu, M. Zhang, H. Dai, C. Wang, D. Ding and Z. Zhong, *J. Control. Release*, 2023, **356**, 623–648.
55 H. Wang, M. Zhang, Y. Ma, B. Wang, H. Huang, Y. Liu, M. Shao and Z. Kang, *ACS Appl. Mater. Interfaces*, 2020, **12**, 41088–41095.
56 F. Li, T. Li, C. Sun, J. Xia, Y. Jiao and H. Xu, *Angew. Chem. Int. Ed. Engl.*, 2017, **56**, 9910–9914.
57 L. Yue, H. Li, Q. Sun, J. Zhang, X. Luo, F. Wu and X. Zhu, *ACS Appl. Nano Mater.*, 2020, **3**(1), DOI: **10.1021/acsanm.9b02394**.
58 M. A. S. Shaik, D. Samanta, M. Shaw, I. Mondal, R. Basu and A. Pathak, *Sens. Actuator. Rep.*, 2022, **4**, 100127.
59 D. L. Sai, J. Lee, D. L. Nguyen and Y.-P. Kim, *Exp. Mol. Med.*, 2021, **53**, 495–504.
60 T. Dai, B. B. Fuchs, J. J. Coleman, R. A. Prates, C. Astrakas, T. G. St Denis, M. S. Ribeiro, E. Mylonakis, M. R. Hamblin and G. P. Tegos, *Front. Microbiol.*, 2012, **3**, 120.
61 Q. Li, X. Shen and D. Xing, *Dyes Pigm.*, 2023, **208**, 110784.
62 T. Zhang, H. Xing, M. Xiong, M. Gu, Z. Xu, L. Zhang, Y. Kang and P. Xue, *Chem. Eng. J.*, 2024, **488**, 150819.
63 J. Xu, L. Xu, C. Wang, R. Yang, Q. Zhuang, X. Han, Z. Dong, W. Zhu, R. Peng and Z. Liu, *ACS Nano*, 2017, **11**, 4463–4474.
64 X. Wu, B. Zhao, J. Zhang, H. Xu, K. Xu and G. Chen, *J. Phys. Chem. C*, 2019, **123**, 25570–25578.
65 I. Liguori, G. Russo, F. Curcio, G. Bulli, L. Aran, D. Della-Morte, G. Gargiulo, G. Testa, F. Cacciatore, D. Bonaduce and P. Abete, *Clin. Interventions Aging*, 2018, **13**, 757–772.
66 C. Dong, S. Wang, M. Ma, P. Wei, Y. Chen, A. Wu, Z. Zha and H. Bi, *Appl. Mater. Today*, 2021, **25**, 101178.
67 S. Podder, C. K. Ghosh, A. Das and J. G. Hardy, *Emergent Mater*, 2022, **5**, 455–475.
68 V. Kiselev, I. Kislyakov and A. Burchinov, *Opt. Spectrosc.*, 2016, **120**, 520–528.
69 J. Wang, N. Tian, T. Tian, L. Xiao, X. Zhou, G. Liu, Z. Zhang, Y. Zhao, J. Guo, Q. Lin and Y. Jiang, *Colloids Surf., B*, 2025, **246**, 114392.
70 N. Tian, X. Liu, X. He, Y. Liu, L. Xiao, P. Wang, D. Zhang, Z. Zhang, Y. Zhao, Q. Lin, C. Fu and Y. Jiang, *RSC Adv.*, 2024, **14**, 36437–36450.
71 T. Boutros, E. Chevet and P. Metrakos, *Pharmacol. Rev.*, 2008, **60**, 261–310.
72 S. Schoonbroodt, V. Ferreira, M. Best-Belpomme, J. R. Boelaert, S. Legrand-Poels, M. Korner and J. Piette, *J. Immunol.*, 2000, **164**, 4292–4300.
73 Y. Takada, A. Mukhopadhyay, G. C. Kundu, G. H. Mahabeleshwar, S. Singh and B. B. Aggarwal, *J. Biol. Chem.*, 2003, **278**, 24233–24241.
74 B. T. Hennessy, D. L. Smith, P. T. Ram, Y. Lu and G. B. Mills, *Nat. Rev. Drug Discov.*, 2005, **4**, 988–1004.
75 C. Zhuang, S. Narayanapillai, W. Zhang, Y. Y. Sham and C. Xing, *J. Med. Chem.*, 2014, **57**, 1121–1126.
76 J. E. Ziello, I. S. Jovin and Y. Huang, *Yale J. Biol. Med.*, 2007, **80**, 51–60.
77 T. J. Guzik and D. G. Harrison, *Drug Discov. Today*, 2006, **11**, 524–533.
78 Y.-M. Go and D. P. Jones, *Free Radic. Biol. Med.*, 2011, **50**, 495–509.
79 Z. He, Q. Xu, B. Newland, R. Foley, I. Lara-Sáez, J. F. Curtin and W. Wang, *J. Mater. Chem. B*, 2021, **9**, 6326–6346.
80 Y. Sheng, I. A. Abreu, D. E. Cabelli, M. J. Maroney, A.-F. Miller, M. Teixeira and J. S. Valentine, *Chem. Rev.*, 2014, **114**, 3854–3918.
81 M. Alfonso-Prieto, X. Biarnés, P. Vidossich and C. Rovira, *J. Am. Chem. Soc.*, 2009, **131**, 11751–11761.
82 K. P. Bhabak and G. Mugesh, *Acc. Chem. Res.*, 2010, **43**, 1408–1419.
83 H. J. Forman, H. Zhang and A. Rinna, *Mol. Aspects Med.*, 2009, **30**, 1–12.
84 M. G. Traber and J. F. Stevens, *Free Radic. Biol. Med.*, 2011, **51**, 1000–1013.
85 P. C. Ikwegbue, P. Masamba, B. E. Oyinloye and A. P. Kappo, *Pharmaceuticals*, 2017, **11**(1), DOI: **10.3390/ph11010002**.
86 C. Kang, Y. Huang, H. Yang, X. F. Yan and Z. P. Chen, *Nanomaterials*, 2020, **10**(11), DOI: **10.3390/nano10112316**.
87 Q. Yang and S. K. Lai, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.*, 2015, **7**, 655–677.
88 B.-M. Chen, T.-L. Cheng and S. R. Roffler, *ACS Nano*, 2021, **15**, 14022–14048.
89 M. O. Alas and R. Genc, *J. Nanoparticle Res.*, 2017, **19**, 185.
90 S. Hussain, J. A. J. Vanoirbeek and P. H. M. Hoet, *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.*, 2012, **4**, 169–183.
91 M. I. Vazquez, J. Catalan-Dibene and A. Zlotnik, *Cytokine*, 2015, **74**, 318–326.
92 S. Gordon and A. Plüddemann, *BMC Biol.*, 2017, **15**, 53.
93 D. A. Chistiakov, V. A. Myasoedova, V. V Revin, A. N. Orekhov and Y. V Bobryshev, *Immunobiology*, 2018, **223**, 101–111.
94 G. Sanità, B. Carrese and A. Lamberti, *Front. Mol. Biosci.*, 2020, **7**, 587012.
95 S. Awate, L. A. Babiuk and G. Mutwiri, *Front. Immunol.*, 2013, **4**, 114.
96 M. Iturralde, M. Ripoll, D. di Silvio, M. Gallego, D. A. Grajales-Hernández, X. López, L. Betancor and F. López-Gallego, *Adv. Funct. Mater.*, 2024, 2406097.
97 L. Wang, R. Yang, B. Yuan, Y. Liu and C. Liu, *Acta Pharm. Sin. B*, 2015, **5**, 310–315.
98 C. M. Scull, W. D. Hays and T. H. Fischer, *J. Inflammation*, 2010, **7**, 53.

99 Y.-Y. Liu, N.-Y. Yu, W.-D. Fang, Q.-G. Tan, R. Ji, L.-Y. Yang, S. Wei, X.-W. Zhang and A.-J. Miao, *Nat. Commun.*, 2021, **12**, 812.
100 Y. Fan, F. Namata, J. Erlandsson, Y. Zhang, L. Wågberg and M. Malkoch, *Pharmaceutics*, 2020, **12**(12), 1139.
101 B. Srinivas Reddy, R. Kiran Kumar Reddy, V. G. M. Naidu, K. Madhusudhana, S. B. Agwane, S. Ramakrishna and P. V Diwan, *J. Ethnopharmacol.*, 2008, **115**, 249–256.
102 A. J. Singer and R. A. Clark, *N. Engl. J. Med.*, 1999, **341**, 738–746.
103 K. B. Narayanan and H. H. Park, *Adv. Colloid Interface Sci.*, 2013, **201–202**, 30–42.
104 M. Zhang, X. Zhai, T. Ma, Y. Huang, C. Yan and Y. Du, *Chem. Eng. J.*, 2021, **423**, 130301.
105 C. H. Lee, S. Y. Song, Y. J. Chung, E. K. Choi, J. Jang, D. H. Lee, H. D. Kim, D.-U. Kim and C. B. Park, *ACS Appl. Bio Mater.*, 2022, **5**, 761–770.
106 M. Karin and H. Clevers, *Nature*, 2016, **529**, 307–315.
107 T. Leigh, R. G. Scalia and M. V Autieri, *Am. J. Physiol.: Cell Physiol.*, 2020, **319**, C457–C464.
108 T. Hussain, B. Tan, Y. Yin, F. Blachier, M. C. B. Tossou and N. Rahu, *Oxid. Med. Cell. Longev.*, 2016, **2016**, 7432797.
109 B. Das, P. Pal, P. Dadhich, J. Dutta and S. Dhara, *ACS Biomater. Sci. Eng.*, 2019, **5**, 346–356.
110 K. J. McHugh, L. Jing, A. M. Behrens, S. Jayawardena, W. Tang, M. Gao, R. Langer and A. Jaklenec, *Adv. Mater.*, 2018, **30**, e1706356.
111 P. C. Ray, S. A. Khan, A. K. Singh, D. Senapati and Z. Fan, *Chem. Soc. Rev.*, 2012, **41**, 3193–3209.
112 Y. Li, X. Zhang, M. Zheng, S. Liu and Z. Xie, *RSC Adv.*, 2016, **6**, 54087–54091.
113 Q. Li, R. Zhou, Y. Xie, Y. Li, Y. Chen and X. Cai, *Cell Proliferation*, 2020, **53**, e12786.
114 S. Madadi, A. Dehghani, M. Hassan, M. Kianinia, I. Aharonovich and V. Gomes, *Chem. Eng. J.*, 2023, **8**(7), DOI: **10.1016/j.cej.2017.07.165**.
115 G. Gedda, Y.-Y. Yao, S.-H. Chen, A. V Ghule, Y.-C. Ling and J.-Y. Chang, *J. Mater. Chem. B*, 2017, **5**, 6282–6291.
116 L. Jiang, H. Cai, W. Qin, Z. Li, L. Zhang and H. Bi, *Bioconjug. Chem.*, 2023, **34**, 1387–1397.
117 J. Ge, Q. Jia, W. Liu, M. Lan, B. Zhou, L. Guo, H. Zhou, H. Zhang, Y. Wang, Y. Gu, X. Meng and P. Wang, *Adv. Healthc. Mater.*, 2016, **5**, 665–675.
118 J. Ge, M. Lan, B. Zhou, W. Liu, L. Guo, H. Wang, Q. Jia, G. Niu, X. Huang, H. Zhou, X. Meng, P. Wang, C.-S. Lee, W. Zhang and X. Han, *Nat. Commun.*, 2014, **5**, 4596.
119 H. Yao, W. Zhao, S. Zhang, X. Guo, Y. Li and B. Du, *J. Mater. Chem. B*, 2018, **6**, 3107–3115.
120 T. G. Dacoba, R. W. Omange, H. Li, J. Crecente-Campo, M. Luo and M. J. Alonso, *ACS Nano*, 2019, **13**, 4947–4959.
121 Z. Fasihi, F. Mehri, H. Ebrahimi, Z. Jamali, E. Khanlou, F. Kahrizi and A. Salimi, *Pharm. Biomed. Res.*, 2020, **5**(4), DOI: **10.18502/pbr.v5i4.2392**.
122 M. Z. Fahmi, W. Sukmayani, S. Q. Khairunisa, A. M. Witaningrum, D. W. Indriati, M. Q. Y. Matondang, J.-Y. Chang, T. Kotaki and M. Kameoka, *RSC Adv.*, 2016, **6**, 92996–93002.
123 S. Huang, J. Gu, J. Ye, B. Fang, S. Wan, C. Wang, U. Ashraf, Q. Li, X. Wang, L. Shao, Y. Song, X. Zheng, F. Cao and S. Cao, *J. Colloid Interface Sci.*, 2019, **542**, 198–206.
124 P. Innocenzi and L. Stagi, *Chem. Sci.*, 2020, **11**, 6606–6622.
125 S.-T. Yang, X. Wang, H. Wang, F. Lu, P. G. Luo, L. Cao, M. J. Meziani, J.-H. Liu, Y. Liu, M. Chen, Y. Huang and Y.-P. Sun, *J. Phys. Chem. C*, 2009, **113**, 18110–18114.
126 A. Łoczechin, K. Séron, A. Barras, E. Giovanelli, S. Belouzard, Y.-T. Chen, N. Metzler-Nolte, R. Boukherroub, J. Dubuisson and S. Szunerits, *ACS Appl. Mater. Interfaces*, 2019, **11**(46), 42964–42974.
127 X. Zhao, J. Zhang, L. Shi, M. Xian, C. Dong and S. Shuang, *RSC Adv.*, 2017, **7**, 42159–42167.
128 J. B. Opalinska and A. M. Gewirtz, *Nat. Rev. Drug Discov.*, 2002, **1**, 503–514.
129 S. Zhu, J. Zhang, C. Qiao, S. Tang, Y. Li, W. Yuan, B. Li, L. Tian, F. Liu, R. Hu, H. Gao, H. Wei, H. Zhang, H. Sun and B. Yang, *Chem. Commun.*, 2011, **47**, 6858–6860.
130 Z.-C. Yang, M. Wang, A. M. Yong, S. Y. Wong, X.-H. Zhang, H. Tan, A. Y. Chang, X. Li and J. Wang, *Chem. Commun.*, 2011, **47**, 11615–11617.
131 J. Peng, W. Gao, B. K. Gupta, Z. Liu, R. Romero-Aburto, L. Ge, L. Song, L. B. Alemany, X. Zhan, G. Gao, S. A. Vithayathil, B. A. Kaipparettu, A. A. Marti, T. Hayashi, J.-J. Zhu and P. M. Ajayan, *Nano Lett.*, 2012, **12**, 844–849.
132 H. Tao, K. Yang, Z. Ma, J. Wan, Y. Zhang, Z. Kang and Z. Liu, *Small*, 2012, **8**, 281–290.
133 M. Zhang, L. Bai, W. Shang, W. Xie, H. Ma, Y. Fu, D. Fang, H. Sun, L. Fan, M. Han, C. Liu and S. Yang, *J. Mater. Chem.*, 2012, **22**, 7461–7467.
134 S. Buroni, S. Pollini, G. M. Rossolini and E. Perrin, *Front. Genet.*, 2019, **10**, 983.
135 D. Al-Shammery, D. Michelogiannakis, Z. U. Ahmed, H. B. Ahmed, P. E. Rossouw, G. E. Romanos and F. Javed, *Photodiagn. Photodyn. Ther.*, 2019, **25**, 456–459.
136 X. Dong, W. Liang, M. J. Meziani, Y.-P. Sun and L. Yang, *Theranostics*, 2020, **10**, 671–686.
137 M. A. Jhonsi, D. A. Ananth, G. Nambirajan, T. Sivasudha, R. Yamini, S. Bera and A. Kathiravan, *Spectrochim. Acta, Part A*, 2018, **196**, 295–302.
138 M. Kováčová, Z. M. Marković, P. Humpolíček, M. Mičušík, H. Švajdlenková, A. Kleinová, M. Danko, P. Kubát, J. Vajďák, Z. Capáková, M. Lehocký, L. Münster, B. M. Todorović Marković and Z. Špitalský, *ACS Biomater. Sci. Eng.*, 2018, **4**, 3983–3993.
139 Y. Yan, W. Kuang, L. Shi, X. Ye, Y. Yang, X. Xie, Q.-S. Shi and S. Tan, *J. Alloys Compd.*, 2019, DOI: **10.1016/j.jallcom.2018.10.191**.