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Harnessing carbon nanomaterials for reactive oxygen species regulation: Insights into generation, scavenging, and sensing☆

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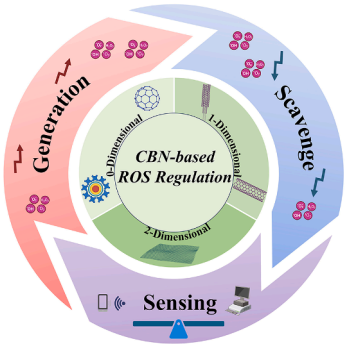
GRAPHICAL ABSTRACT



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ABSTRACT

Carbon nanomaterials (CBNs) have driven significant research advances in medicine over the past decades due to their unique structures and properties. In particular, the role of CBNs in regulating reactive oxygen species (ROS) has been extensively studied recently. ROS, primarily comprising free radicals and non-radical species of oxygen, are recognized as critical byproducts of cell metabolism. ROS level is vital for local cell and tissue homeostasis, facilitating cell–cell communication, and stabilizing the redox system under normal conditions. However, excessive accumulation of ROS can cause oxidative stress, leading to aging and serious pathologies. As a result, the regulation of ROS in various diseases has garnered significant attention. In this regard, understanding the interaction of CBNs with ROS is critical for their biomedical applications. This review article highlights the dual role of ROS in the tissue microenvironment and emphasizes the significance of the structure–property relationship of CBNs in regulating ROS. It further identifies emerging trends in recent studies on CBN-based ROS regulation including generation, scavenging, and sensing. Specifically, the potential for dynamic modulation of the tissue microenvironment through the combined generation and scavenging of ROS is highlighted. Finally, future perspectives are presented, focusing on the biosafety and potential clinical applications of CBNs, as well as recent advances in sensing technologies and insights into redox biology. Together, these insights aim to provide a foundation for designing CBN-based biomaterials for both ROS therapeutic and monitoring applications.

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1. Introduction

Carbon nanomaterials (CBNs) have garnered significant attention due to their unique physicochemical properties, versatility, and wide range of applications in biomedical, environmental, and energy fields [1,2]. Most of the CBNs share some common features that distinguish them from other nanomaterials, such as a backbone composed of sp^2/sp^3 hybridized carbon atoms and high π-electron delocalization. Their nanoscale dimensions further confer a high relative surface area and possible quantum mechanical characteristics [3]. Additionally, carbon atoms can arrange themselves in various configurations to form different types of CBNs, such as fullerenes [4], carbon nanotubes (CNTs) [5], graphene/graphene oxide (GO) [6], and carbon dots (CDs) [7], which exhibit a combination of exceptional properties. These properties, including their electrochemical characteristics and photoluminescence [8,9], are particularly relevant to the biomedical field. For example, researchers could leverage the superior conductivity, electrochemical properties, and high mechanical strength of CNTs to fabricate nanoscale bioelectrode and electrochemical enzyme biosensors [10]. Similarly, the unique fluorescence properties and excellent biocompatibility of CDs have made them suitable to be used in various biomedical devices, particularly for fluorescence imaging applications [11]. The structural diversity of CBNs allows researchers to tailor and optimize their designs to meet the specific requirements of various biomedical applications [12].

Recently, there has been growing attention on understating the role of CBNs in regulating reactive oxygen species (ROS). ROS are byproducts generated during normal cell metabolism, consisting primarily of non-radical species like hydrogen peroxide (H_2O_2), singlet oxygen molecules ($^1O_2$), as well as free radical species such as superoxide anions ($O_2^{\bullet-}$) and hydroxyl radicals ($OH^{\bullet}$) [13]. ROS in the human body has two main functions. At normal levels, they help with cell signaling and support tissue homeostasis by making cells more resilient to environmental changes [14]. Nevertheless, excessive ROS production could result in damage of protein/DNA/lipids within cell structures, leading to irreversible aging [15], or serious pathogenesis like inflammation/immune disorders [16,17] and neurodegeneration [18]. However, in certain conditions, such as cancer or infections caused by bacteria, fungi, or viruses, excessive ROS can be beneficial. They facilitate the elimination of tumor cells and pathogens, restoring balance to the local environment [19–21]. Therefore, regulating ROS levels according to the type and stage of a disease is crucial for developing next-generation therapeutics that restore and maintain normal cellular and tissue functions. Generating or scavenging ROS can be used to modulate ROS concentration in the microenvironment, while implementing real-time sensing techniques is crucial for monitoring ROS dynamics, enabling precise modulation. This approach mirrors the clinical management of diabetes, where a glucometer is used to monitor blood sugar levels in real-time, allowing for timely insulin administration to maintain glucose balance [22]. Similarly, real-time ROS sensing provides immediate data, facilitating dynamic regulation of ROS levels to prevent cellular damage and promote overall health.

In this context, we highlight the multifaceted role of CBNs in ROS regulation, encompassing three critical aspects: generation, scavenging, and sensing/monitoring [23,24]. Due to their unique properties, CBNs emerge as one of the ideal materials for ROS regulation to effectively address all these three key elements (Fig. 1). CBNs possess delocalized π-electrons and specific side functional groups, such as carboxyl (-COOH), carbonyl (-C=O), and hydroxyl (-OH) group, which enable them to directly interact with ROS and function as scavengers [25–28]. Additionally, certain CBNs like CNTs can be activated by external stimuli, such as light or ultrasound, to generate ROS via photochemical reactions [29,30]. These materials can also interact directly with pathogens to induce intracellular ROS generation [31]. Furthermore, due to their superior conductivity and photoluminescence properties, certain CBNs, such as CDs, are suitable for fabricating ROS sensors. These sensors enable real-time monitoring of ROS levels through electrochemical or fluorescence-based methods [24,32]. These features underscore the immense potential of CBNs for tailored designs in ROS regulation. Therefore, a comprehensive understanding of CBN's interactions with ROS is essential for their safe and effective utilization in medicine. This review delves into various categories of CBNs involved in ROS regulation, examines the biological roles of ROS, and explores the structure–property relationships of CBNs related to ROS generation and scavenging. We also discuss the mechanisms of CBN-based ROS sensing and provide perspectives on the biosafety and critical challenges associated with applying CBNs in ROS regulation, outlining future directions to address emerging challenges in this field.

2. Carbon nanomaterials and their functional categories

CBNs are classified based on their dimensionality into zero-dimensional (0D), one-dimensional (1D), and two-dimensional (2D) structures [33], each offering unique properties and functionalities that can be tailored for specific ROS-related applications. In this section, we will introduce various CBNs based on their dimensional categories and discuss their fundamental characteristics for ROS regulation.

2.1. Zero-dimensional (0D) carbon nanomaterials

The 0D CBNs are characterized by nanoscale dimensions in all directions, resulting in spherical or nearly spherical structures [34]. CDs represent a prominent example of 0D CBNs, which involve carbon quantum dots (CQDs), graphene quantum dots (GQDs), carbon nanodots (CNDs), and polymer dots (PDs) [35]. CDs are typically composed of amorphous or crystalline sp^2-hybridized carbon cores surrounded by functional groups, such as -OH, -COOH and amine groups (-NH, $-NH_2$), which enhance their solubility and reactivity [36]. These functional groups also contribute to their remarkable photoluminescence, enabling their use in bioimaging and ROS sensing. Fullerenes, another class of 0D CBNs, consists of cage-like molecules such as C_{60}, where sp^2-hybridized

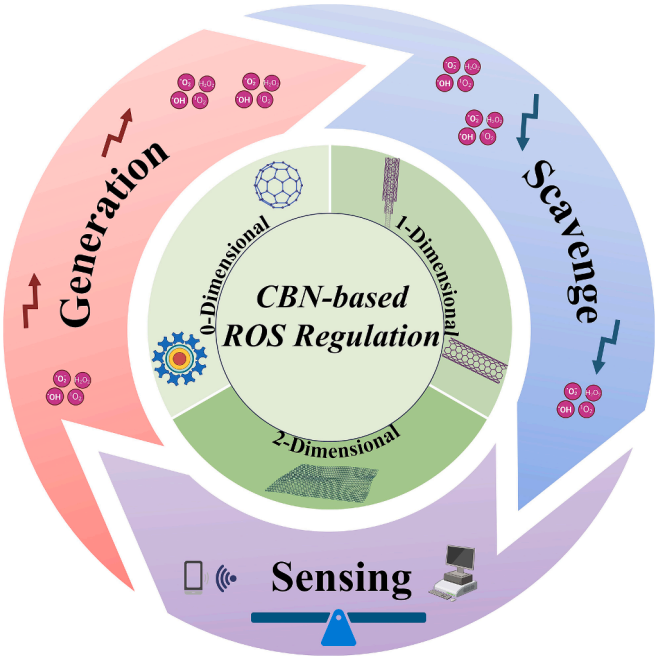

Fig. 1. Schematics of regulation of reactive oxygen species (ROS) using various carbon nanomaterials (CBNs): Different dimensions of CBNs and their ROS modulation by either generating or scavenging ROS, depending on their specific properties and applications. Real-time sensing techniques for monitoring ROS dynamics, enabling precise modulation and maintaining a balance between ROS generation and scavenging. [Generated from Biorender].

carbon atoms form a closed-shell configuration with hexagonal and pentagonal rings [37]. Fullerenes exhibit unique electron-accepting properties, making them effective in ROS scavenging and antioxidant applications. The detailed mechanism of fullerenes-based ROS scavenging will be covered in the CBN-based ROS scavenging section. Along with CDs and fullerenes, carbon nano-onions and carbon nanodiamonds also represent 0D CBN structures; however, limited studies are available based on their application in medical field [34,38].

2.2. One-dimensional (1D) carbon nanomaterials

The 1D CBNs exhibit extended dimensions in one direction, with the other two confined to the nanoscale [39]. CNTs are the most widely studied 1D CBNs, featuring cylindrical structures formed by rolling graphene sheets into seamless tubes. Depending on the number of graphene layers, CNTs are classified as single-walled (SWCNTs) or multi-walled (MWCNTs) [40]. CNTs possess exceptional mechanical strength, electrical conductivity, and large surface area, making them ideal for engineering biosensors with structural stability and robust sensitivity for ROS sensing and electrochemical applications. Carbon nanofibers (CNFs) are another example of 1D CBNs, characterized by stacked graphene layers in various orientations [41]. These materials are highly conductive and mechanically robust, enabling their integration into ROS-regulating devices.

2.3. Two-dimensional (2D) carbon nanomaterials

The 2D CBNs have a single nanoscale dimension, with extended lateral dimensions, making them ideal for applications requiring large surface areas [42]. Graphene, the archetype of 2D CBNs, consists of a single layer of sp^2-hybridized carbon atoms arranged in a honeycomb lattice [38]. Its exceptional electrical conductivity, mechanical strength, and thermal stability enable precise ROS sensing. GO, a chemically modified derivative of graphene [43], contains oxygenated functional groups such as -OH, epoxy, and -COOH. These groups enhance GO's solubility and reactivity, making it effective for ROS scavenging and catalytic applications. For example, -C=O may act as catalytic sites for enzyme-like ROS scavenging [27], as well as the catalytically active sites for enzyme-like toxic ROS generation [44]. Nevertheless, the formation of GO may undermine the conductivity of graphene because of the disruption of the conjugation system by the oxygen-containing groups [45]. Reduced graphene oxide (rGO) [43], formed by reducing GO, partially restores the electrical conductivity of graphene, balancing chemical groups' functionality with conductivity for ROS regulation. Graphitic carbon nitride (g-C_3N_4), with its polymeric nature and similar structure to graphene, is considered the next-generation organic-like semiconductor with high biocompatibility and photo-catalyzing properties [46,47]. In addition, due to its nitrogen-doping-graphene-like structure and its wide applications in ROS-related biofields, g-C_3N_4 can be introduced as a special type of CBN as they have similar characteristics to CBNs [46,48,49],

The diverse structural categories of CBNs highlight their multifunctional roles in ROS regulation. By harnessing their unique properties, CBNs offer innovative solutions for sensing, generating, and scavenging ROS, contributing significantly to advancement in their biomedical and environmental applications.

3. Introduction of reactive oxygen species (ROS)

Understanding ROS, including their nature, biological origins, and functions, is essential for effectively leveraging CBNs in ROS regulation. This foundational knowledge enables scientists to develop targeted strategies for ROS sensing, generating, and scavenging. ROS are chemically reactive molecules containing oxygen, such as $O_2^{\bullet-}$, H_2O_2, $OH^{\bullet}$, and $^1O_2$, which are generated as natural byproducts of cellular metabolism, particularly during mitochondrial oxidative phosphorylation [50]. While essential for physiological processes such as signaling, immune defense, and cellular homeostasis, excessive ROS can cause oxidative stress, leading to cellular damage, aging, and a range of diseases. In this section, we will provide a concise overview of the sources of ROS and their biological functions.

3.1. Origins of ROS: endogenous vs. exogenous sources

The origins of ROS can be classified into two main categories: endogenous and exogenous sources. Endogenous ROS are primarily produced within the body as byproducts of normal cellular processes, such as mitochondrial respiration. Exogenous ROS, on the other hand, are introduced from external factors like environmental pollutants, radiation, and pathogens, contributing to oxidative stress and cellular damage. Understanding these origins is crucial for developing effective strategies to regulate ROS for various biomedical applications.

3.1.1. Endogenous ROS sources

Endogenous production of ROS occurs through diverse mechanisms across various cellular compartments, reflecting their complex roles in maintaining physiological functions and contributing to pathological processes. Among the primary sources, mitochondria are a major source of ROS. Species like $O_2^{\bullet-}$ are being produced during oxidative phosphorylation when some electrons leak from the electron transport chain. This quickly converts to H_2O_2 by superoxide dismutase (SOD), preventing damage and enabling ROS to function in cell signaling [51]. Mitochondrial ROS (mtROS) regulate processes like mitochondrial repair, stress responses, and cell signaling. However, excessive mtROS can damage mitochondrial DNA, proteins, and lipids, contributing to diseases like neurodegeneration, heart problems, and metabolic disorders [18]. Thus, maintaining a balance of ROS is essential for cellular health. Another significant source of endogenous ROS is the peroxisome, an organelle involved in β-oxidation of fatty acid and the metabolism of reactive compounds [52]. Peroxisomal oxidation processes generate H_2O_2 as a byproduct, which is regulated by catalase (CAT), a peroxisomal enzyme that converts H_2O_2 into water (H_2O) and oxygen (O_2). This enzymatic activity maintains cellular redox balance, but dysregulation can also lead to oxidative stress and associated pathologies [53]. Peroxisomal ROS also play signaling roles, influencing processes such as lipid metabolism and cellular aging. NADPH oxidases (NOX), a family of membrane-bound enzymes, are another ROS source [54]. NOX enzymes produce superoxide in response to external stimuli, such as growth factors, cytokines, or pathogens, making them essential players in immune defense, redox signaling, and vascular homeostasis. In immune cells like neutrophils and macrophages, NOX-mediated ROS production forms part of the respiratory burst, a process critical for destroying pathogens. Beyond immune functions, NOX enzymes are involved in regulating vascular tone, cell migration, and wound healing. Dysregulation of NOX activity, however, has been implicated in inflammatory diseases, cancer progression, and endothelial dysfunction [54]. Other enzymes, including xanthine oxidase [55], cytochrome P450 enzymes [56], lipoxygenases [57], and cyclooxygenases [58], contribute to ROS production during normal and stress-induced metabolic activities. For example, xanthine oxidase generates ROS during purine metabolism, particularly in ischemia–reperfusion injury, where oxygen restoration after a period of deprivation triggers excessive ROS production and tissue damage. Cytochrome P450 enzymes, involved in the detoxification of xenobiotics and drug metabolism, inadvertently produce ROS during electron leakage from their catalytic cycle. Similarly, while lipoxygenases generate ROS, metabolizing polyunsaturated fatty acids influences inflammation and eicosanoid signaling. The endoplasmic reticulum (ER) also acts as a critical ROS-generating compartment [59]. During protein folding, the formation of disulfide bonds, catalyzed by protein disulfide isomerases, produces H_2O_2 as a byproduct. Under normal conditions, the ER's antioxidant defenses manage ROS production, supporting its essential role in protein maturation. However, ER

stress, triggered by protein misfolding or an overload of unfolded proteins, exacerbates ROS generation. This creates a feedback loop linking ROS with unfolded protein responses (UPR), which, if unresolved, leads to cellular dysfunction and apoptosis. ER stress-induced ROS are increasingly recognized as contributors to diseases such as diabetes, neurodegeneration, and cancer [59].

3.1.2. Exogenous ROS sources

The endogenous production of ROS highlights their role as natural byproducts of cellular metabolism, tightly regulated to support physiological processes such as signaling, adaptation, and defense. However, this finely tuned balance is frequently disrupted by exogenous sources of ROS, which exacerbates oxidative stress and amplifies the effects of endogenous ROS. Exogenous ROS arise from environmental exposures, toxins, and pathogens, introducing additional oxidative challenges that impact cellular and systemic redox homeostasis. Environmental factors are among the most common exogenous sources of ROS. Ultraviolet (UV) radiation from sunlight and ionizing radiation from medical imaging or environmental exposure directly generate ROS by causing the radiolysis of H_2O [60]. These ROS, including $OH^{\bullet}$ and $^1O_2$, induce significant damage to DNA, lipids, and proteins, contributing to skin aging, inflammation, and carcinogenesis [61]. Similarly, airborne pollutants such as particulate matters and ozone (O_3) stimulate ROS production in respiratory tissues, exacerbating conditions like lung carcinogenesis [62], asthma [63], chronic obstructive pulmonary disease (COPD) [64], and cardiovascular disease [64]. Similarly, cigarette smoke, containing a complex mixture of free radicals and chemical irritants, dramatically increases ROS levels in the lungs [65], promoting oxidative damage, inflammation, and the development of cancer [66]. In addition, toxins and xenobiotics, including heavy metals and certain pharmaceuticals [67], also significantly contribute to exogenous ROS production. Heavy metals like arsenic (As), cadmium (Cd), and mercury (Hg) induce ROS through redox cycling or by depleting cellular antioxidants, such as glutathione [68]. This disruption of redox balance leads to oxidative stress, which underlines the toxicity of these metals, manifesting in conditions such as neurodegeneration, kidney damage, and cancer. Similarly, drugs like doxorubicin, a widely used chemotherapeutic agent, generate ROS as a part of their therapeutic action against cancer cells. However, this ROS production also causes significant off-target toxicity, particularly in cardiac tissues, where oxidative stress damages mitochondria and contributes to cardiomyopathy [69].

By combining endogenous and exogenous sources, the cellular redox environment becomes a dynamic interplay between natural metabolic processes and external stressors. Thus, understanding the interaction between these ROS sources is critical for unraveling their contributions to oxidative stress, disease progression, and therapeutic opportunities. As endogenous and exogenous ROS shape cellular fate and tissue health, targeting both sources through proper strategies and regulatory interventions becomes essential for mitigating their combined impacts on human health.

3.2. The dual roles of ROS: physiological and pathogenic functions

ROS play a dual role in cellular functions, serving both physiological and pathogenic purposes. At normal levels, ROS are essential for processes such as cell signaling, immune response, and maintaining tissue homeostasis. However, when overproduced, ROS can induce oxidative stress, contributing to tissue damage and the development of various diseases, highlighting their complex role in health and disease. In this section, we delve into the dual roles of ROS, examining their physiological functions and their involvement in pathological processes.

3.2.1. Physiological roles of ROS

ROS are pivotal in regulating physiological processes, serving as signaling molecules and mediators when maintained within controlled levels. ROS can act as essential players in cellular communication and homeostasis while also posing a threat if dysregulated [70]. As secondary messengers in redox signaling pathways, ROS regulate key processes by oxidizing cysteine residues in target proteins, altering their activity and function [71]. For instance, ROS modulate epidermal growth factor receptor (EGFR), controlling cell proliferation and differentiation [72]. They also activate pro-apoptotic proteins to regulate programmed cell death, ensuring proper development and the removal of damaged cells [73]. Additionally, ROS stimulate autophagy, a vital mechanism that clears damaged organelles and maintains cellular homeostasis [74], highlighting their protective roles under stress. ROS also play a critical role in immune defense mechanisms. During the respiratory burst, immune cells like neutrophils and macrophages produce substantial amounts of ROS via NOX [75]. ROS act as powerful antimicrobial agents, targeting and neutralizing pathogens by disrupting their membranes, denaturing proteins, and damaging DNA. This mechanism highlights the critical role of ROS in host defense and innate immune responses. Beyond their roles in immediate cellular functions, ROS influence broader developmental and adaptive processes. For example, controlled ROS levels guide stem cell differentiation, angiogenesis, and organogenesis [76], emphasizing their significance in developmental biology. Furthermore, ROS enable cells to adapt to stress by activating protective pathways such as nuclear factor erythroid 2-related factor 2 (NRF2)-dependent antioxidant responses, which upregulate genes involved in oxidative stress resistance and detoxification [77]. This adaptive capacity of ROS underscores their physiological significance and aligns with the concept of hormesis. Hormesis refers to the phenomenon where low levels of stressors, including ROS, activate adaptive responses that enhance cellular resilience and promote protection against oxidative stress. This is evident in exercise-induced ROS production, where transient oxidative stress improves mitochondrial function and overall cellular health [14]. This adaptive response not only strengthens cellular defenses but also highlights the importance of maintaining ROS within optimal levels to balance their physiological and pathological effects.

3.2.2. Pathological roles of ROS

Excessive production of ROS or insufficient antioxidant defenses disrupt the delicate balance required for cellular health, leading to oxidative stress. This condition, characterized by an overabundance of ROS, causes widespread damage to cellular macromolecules and contributes to the development and progression of numerous diseases. Oxidative stress targets lipids, proteins, and DNA, causing profound structural and functional alterations. In this context, cellular and organelle membranes, rich in polyunsaturated fatty acids (PUFAs), are particularly susceptible to ROS-induced damage, known as lipid peroxidation. This process generates reactive aldehydes like malondialdehyde (MDA), which compromise membrane integrity [78]. Proteins are similarly vulnerable [79] as oxidation of amino acid residues may lead to enzyme inactivation, disrupted signaling, and aggregation of damaged proteins [80]. Additionally, ROS-induced DNA damage, including strand breaks and oxidative base modifications like 8-oxo-deoxyguanosine (8-oxo-dG), results in genomic instability [81], and ultimately contributes to mutation and cell cycle dysregulation. These cumulative effects of ROS-induced damage are central to the free radical theory of aging, which suggests that oxidative stress speeds up cellular aging and tissue degeneration. Recent studies reveal a more nuanced role for ROS in aging, as they also regulate key longevity pathways involving Forkhead box O (FOXO) transcription factors, and the mechanistic target of rapamycin (mTOR) [82]. While ROS contribute to the degenerative aspects of aging, their role in adaptive stress responses suggests a dual influence on lifespan and health span.

ROS are also key contributors to disease pathogenesis, with their impact varying according to the type and stage of the disease. For instance, in cancer, the ROS contribute to tumor initiation by inducing DNA mutations and genomic instability, while also promoting tumor progression by modulating angiogenesis, invasion, and metastasis [83].

Interestingly, cancer cells, which typically produce elevated levels of ROS, rely on strong antioxidant systems for survival. This presents a therapeutic opportunity to exploit their vulnerability through targeted ROS modulation. Similarly, in neurodegenerative disorders like Alzheimer's, Parkinson's, and Huntington's diseases, ROS exacerbate protein misfolding, mitochondrial dysfunction, and neuronal death, promoting disease progression and cognitive decline [84]. Cardiovascular diseases are also major ROS-associated conditions. ROS contribute to atherosclerosis, hypertension, and ischemia–reperfusion injuries by damaging endothelial cells [85], promoting inflammation, and disrupting vascular homeostasis. In addition, in metabolic disorders such as diabetes, ROS impair insulin signaling, exacerbating insulin resistance and β-cell dysfunction [86]. They also underlie diabetic complications, including neuropathy, nephropathy, and retinopathy, through oxidative damage to blood vessels and tissues [87]. Chronic inflammation is another domain where persistent ROS production plays a destructive role [88]. Conditions such as rheumatoid arthritis [89], inflammatory bowel disease [90], and COPD [91], are fueled by a feedback loop of ROS-driven inflammation and tissue damage. In these diseases, ROS amplify inflammatory signaling, recruit immune cells, and perpetuate tissue injury, leading to progressive dysfunction.

The inherent duality of ROS, exerting beneficial effects at physiological levels (oxidative eustress) and harmful effects at elevated concentrations (oxidative distress), underscores the critical importance of maintaining redox balance for healthy cellular and tissue function [92,93]. This understanding has given rise to the field of redox medicine, which focuses on restoring cellular homeostasis by directly detoxifying reactive intermediates or triggering cytoprotective and antioxidant signaling pathways. Redox medicine utilizes oxidative eustress to regulate redox signaling and maintain proper cellular functions. At the same time, it addresses oxidative distress to prevent pathological cell loss and facilitate the targeted elimination of damaged cells in disease contexts [94]. The limited success of previous attempts to prevent or treat diseases using exogenous antioxidants, such as vitamin C and polyphenols, underscores the need for more effective redox-based therapeutic approaches for clinical translation [95]. A promising approach to achieving such regulation is through the use of CBNs, which have demonstrated considerable potential in mediating ROS generation and scavenging (Fig. 2). In the following section, we will explore how CBNs can facilitate ROS generation and modulation, shedding light on their potential applications in therapeutic contexts.

4. CBN-mediated ROS generation: mechanisms, modulation, and therapeutic potential

The ability of CBNs to generate ROS (with or without external stimuli) has garnered significant interest due to their potential applications in therapeutics e.g., cancer therapy, infection control, and tissue regeneration. The unique structures of CBNs and their interactions with biological systems both play a critical role in the ROS generation process. Mechanistically, CBNs can generate ROS via two primary mechanisms (Fig. 3): direct generation by the nanomaterials themselves or indirect generation through interactions with cellular components. Modulation of these mechanisms (e.g., through alteration of side groups, heteroatom doping, defect manipulation, etc.) to optimize the ROS-generation potential of CBNs is the key to enhancing their therapeutic efficacy. In this section, we will explore the mechanisms of CBN-mediated ROS generation and discuss their modulation strategies and therapeutic applications. The related information is summarized in Table 1.

4.1. Mechanisms of ROS generation induced by CBNs

CBNs can generate ROS through multiple mechanisms, broadly categorized into direct and indirect induction. In direct induction, CBNs produce ROS either autonomously or with external stimulation. In indirect induction, CBNs modulate cellular processes that subsequently lead to ROS generation.

4.1.1. Mechanisms of direct ROS induction by CBNs

The most common approach to directly induce ROS is through external wave stimulation. This mainly includes photo-induced, photocatalytic, sono-induced, and microwave-assisted pathways [29,117,127,140]. Over the past decade, photoinduced, or so-called photodynamic therapy (PDT)-based ROS generation, has remained the primary methodology [114,128]. CBNs can be a replacement for conventional photosensitizers, which absorb light energy and transfer electrons or energy to O_2 in adjacent regions, thereby producing ROS. Photo-induced generation of $^1O_2$ and other radicals has been observed in fullerenes [30,109,110], CNTs [111,112], graphene [114–116], and CDs [29,117–120].

The detailed process for wave-induced ROS generation, including the transition between different energy states, is illustrated in Fig. 4**a**. In this mechanism, CBNs absorb photon energy, causing a transition of electrons from the ground electronic state (S_0) to the excited state (S_1). Some of these electrons then undergo radiative or non-radiative emission, releasing energy such as fluorescence or heat before returning to the ground state. A significant portion, however, undergoes intersystem crossing (ISC) to the triplet excited state (T_1), from where they return to the ground state by transferring electrons or energy to O_2, often accompanied by phosphorescence. In the Type-I pathway, electrons are transferred to O_2, forming $O_2^{\bullet-}$ (**reaction (1)**), and $O_2^{\bullet-}$ can undergo

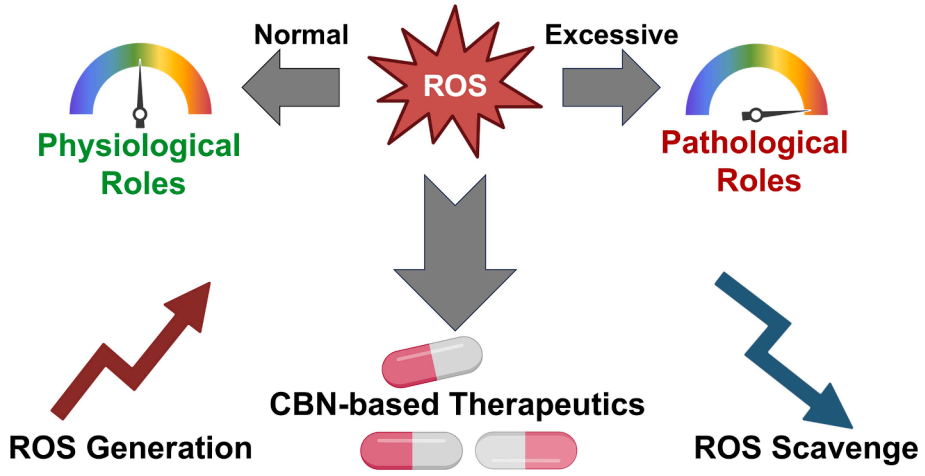

Fig. 2. Dual role of ROS in health and disease, as well as the role of CBNs in modulating ROS levels. [Generated from Biorender].

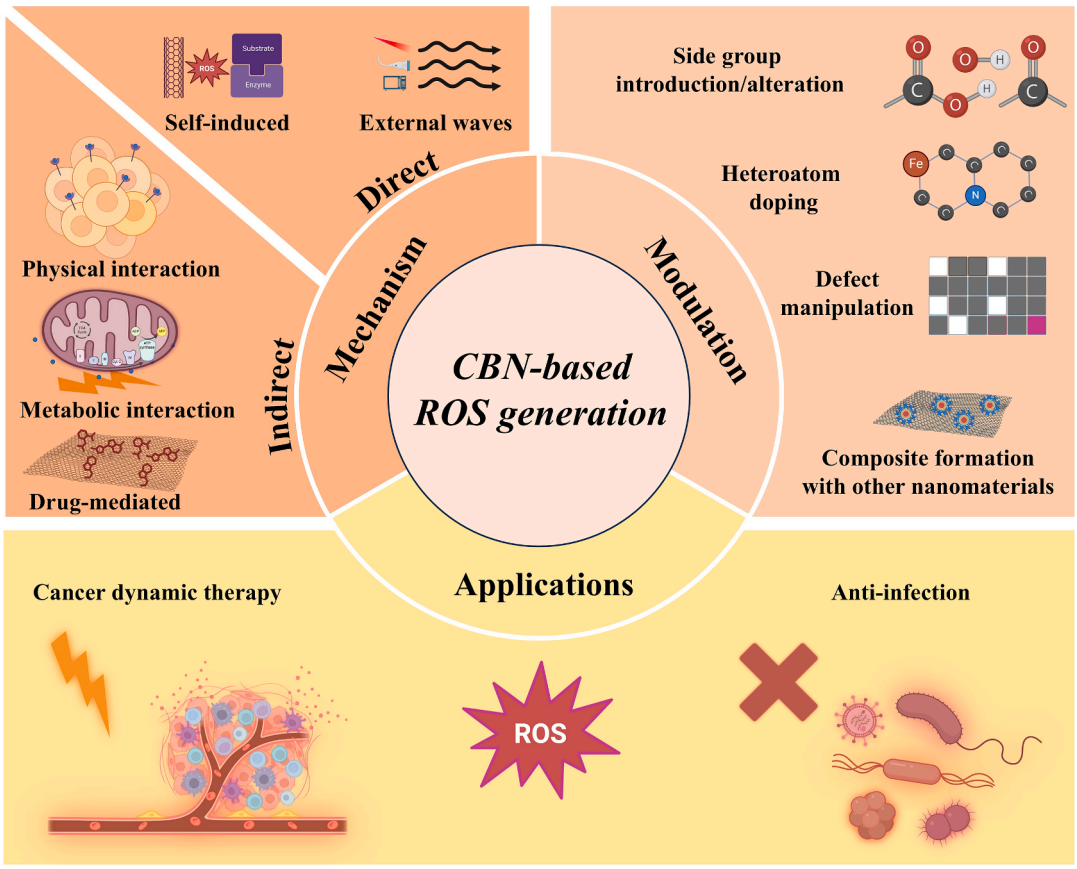

Fig. 3. Mechanism, modulation strategies, and applications of CBNs for ROS generation. [Generated from Biorender].

Table 1
Summary of CBN-based ROS generation strategies.

Mechanisms		Modulations	Nanomaterial types	Applications	References
Direct	Self-induced	Side group introduction/alteration, defect manipulation, heteroatom doping, composite formation	CNTs, CDs, graphene/rGO	Antimicrobial, cancer therapy	[44,96,97,98,99,100,101,102,103,104,105,106,107,108]
	Photo-induced	Side group introduction/alteration, heteroatom doping	Fullerenes derivatives	Antimicrobial	[30,109,110]
			CNTs	Cancer therapy, antimicrobial	[106,111,112,113]
			graphene	Cancer therapy	[114,115,116]
			CDs	Cancer therapy, antimicrobial	[29,117,118,119,120,121,122,123,124,125,126]
	Photocatalytic	Heteroatom doping, defect manipulation	C_3N_4, GO	Antimicrobial, corneal crosslinking therapy	[105,127,128,129,130,131,132,133,134,135]
	Sono-induced	Heteroatom doping, side group introduction/alteration, defect manipulation	CDs, fullerenes derivatives, C_3N_4	Antimicrobial, cancer therapy	[136,137,138,139]
	Microwave assisted	Composite formation	CNTs,	Antimicrobial (Osteomyelitis)	[114,140,141]
Indirect	Physical interaction	N/A	GO/rGO	Antimicrobial	[31,96,142,143,144]
	Metabolic interaction	Composite formation, heteroatom doping	CNTs, GO/rGO	Antimicrobial	[31,143,145,146,147,148,149,150]
	Drug mediated	Composite formation	GO, CDs	Cancer therapy, antimicrobial	[151,152,153]

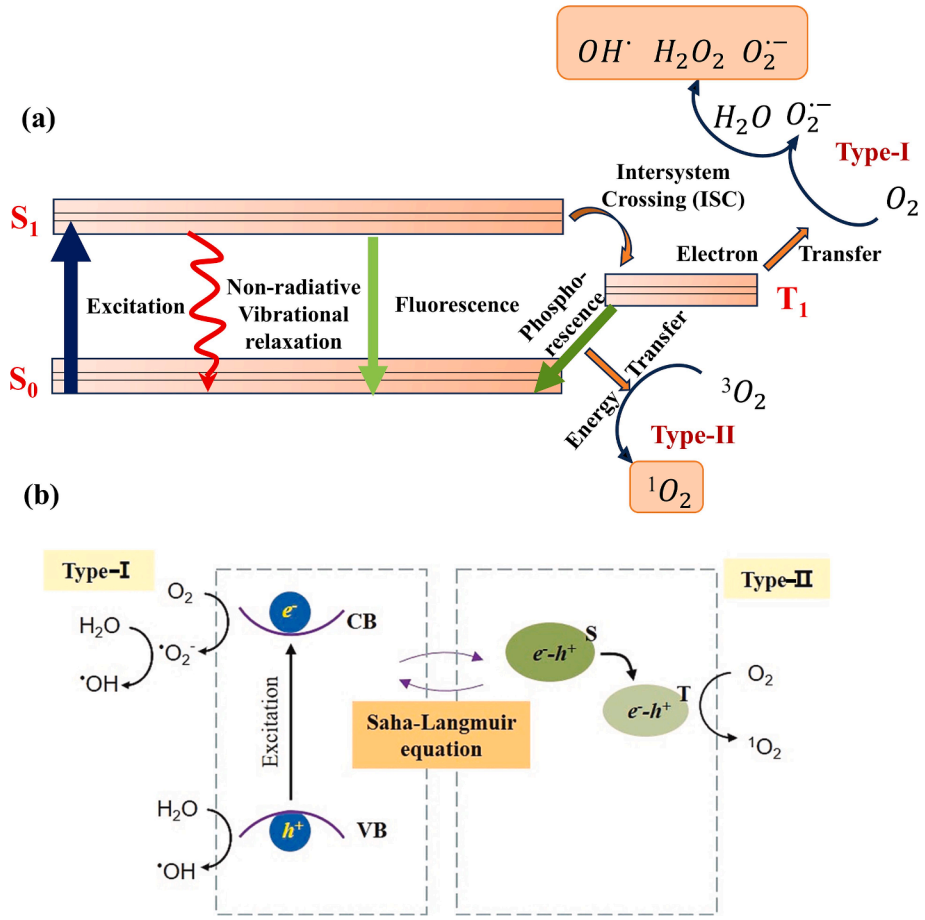

Fig. 4. Mechanisms of wave-induced ROS generation by CBNs: (a) Photon-induced Type-I (electron transfer to oxygen molecules) and Type-II (energy transfer to oxygen molecules) reactions. During the transition of electrons into three energy states: ground state (S_0), excited state (S_1), and triplet excited state (T_1), all forms of ROS can be generated during this process. **(b)** Semiconductor-like catalytic effects through Type-I and Type-II pathways. Under photon excitation, the electron-hole pairs could be induced and participate in the generation of ROS. Reproduced with permission from [128] Copyright 2023, Elsevier.

dismutation and be converted to H_2O_2 and O_2 (**reaction (2)**). Subsequently, the partial reduction of H_2O_2 would result in the formation of $OH^{\bullet}$ (**reaction (3)**). Therefore, through the Type-I pathway, ROS including $O_2^{\bullet-}$, H_2O_2, $OH^{\bullet}$ are mainly formed.

$$O_2 + e^- \rightarrow O_2^{\cdot-} \quad (1)$$

$$2O_2^{\cdot-} + 2H^+ \rightarrow H_2O_2 + O_2 \quad (2)$$

$$H_2O_2 + e^- \rightarrow OH^- + OH^{\cdot} \quad (3)$$

For the Type-II pathway, energy is transferred to O_2, generating $^1O_2$. Here, the triplet ground state ($^3\sum_g^-$) of $^3O_2$, characterized by two separate occupied antibonding orbitals with parallel spins, transits to singlet excited states. The singlet excited states mainly include $^1\Delta_g$, which is characterized by paired-spin electrons occupied in one orbital, and $^1\sum_g^+$ characterized by two unpaired electrons occupied by different antibonding orbitals. For specific CBNs like GQDs, $^1O_2$ could also be generated during ISC, where a higher quantum yield than normal conditions is observed [120]. During the type-II pathway, highly reactive $^1O_2$ is mainly generated. In the hypoxic environment, Type-I reaction which is less oxygen-dependent would dominate, whereas, in a relatively high oxygen supply environment, Type-II which is highly oxygen-dependent would dominate [29]. The $^1O_2$ formed through Type-II is generally considered the main source for bio-related PDT applications. Therefore, significant efforts have been made to develop various oxygen-supplying approaches in conventional PDT applications to promote $^1O_2$ generation [23].

Photocatalytic effects could be induced by some CBNs, which generally act as semiconductors (e.g. g-C_3N_4, CDs, CNTs, GO, and their composites). As shown in Fig. 4**b** [128], under photon activation, the electrons are excited from the valence band to the conduction band, resulting in charge separation and leaving a hole in the valence band. The generated electrons can then perform a reaction similar to **reaction (1)** in Type-I to generate $O_2^{\bullet-}$, while active holes can interact with H_2O to produce $OH^{\bullet}$ (**reaction (4)**) [127,129,130].

$$H_2O + h^+ \rightarrow OH^{\cdot} + H^+ \quad (4)$$

Similar to photon-based pathways, ultrasound irradiation, and microwave induction could also stimulate ROS generation. In these approaches, CBNs can function as the sono-sensitizer or microwave-sensitizer [114,140]. The mechanism of sono-induction involves ultrasound, creating sono-luminescence through inertial cavitation. This process activates CBNs, enabling them to produce ROS through two pathways: Type-I, which involves electron or proton transfer, and Type-II, which involves energy transfer to O_2 [136]. For microwave-induction, the longer wavelength of microwaves compared to visible light allows for deeper tissue penetration. CBNs, such as graphene or CNTs, can absorb microwave energy due to their conductive properties, converting it into localized electric fields. The resulting free electrons and dissipated energy interact with nearby O_2 and H_2O, leading to the generation of ROS [140,141].

While many CBNs require external stimulation to generate ROS, some could catalyze ROS generation independently [117]. The possible mechanism behind this self-generation is diversified. For example, CBNs

like graphene can absorb O_2 at its edge and defect, directly converting it into ROS [96]. Another notable example is the peroxidase (POD)-mimicking activity of CBNs, such as functionalized CNTs or modified CDs. These materials can catalyze Fenton-related reactions, generating $OH^{\bullet}$ in the presence of H_2O_2, thereby amplifying ROS production [97–102,117].

4.1.2. Mechanisms of indirect ROS generation by CBNs

Due to their nanoscale sizes and unique dimension-endowed structural properties, some CBNs can interact with cellular components to induce intracellular ROS generation [31,96,142–144,154]. For example, hydrophobic rGO can be absorbed onto cell membranes and induce intracellular ROS generation through physical interactions [143]. Similarly, GO, with a specific orientation, such as sharp edges positioned against the membrane, tends to induce a higher level of intracellular ROS [31].

In addition to physical contact, interactions related to metabolic manipulation may also induce inner cellular ROS generation and accumulation. This phenomenon is probably attributed to the unique electronic properties of some CBNs, like graphene and CNTs, which feature delocalized π-orbital electrons and electron-trapping defect sites, and electron-withdrawing/repelling side groups [31,143,145–148]. One possible underlying mechanism for the inner cellular ROS generation is that CBNs can function as a highly conductive external electron acceptor or electron sink to pull some of the electrons from the original electron transport chain during cellular respiration in the mitochondria/bacteria membrane, disrupting the homeostasis of cell metabolism and thus leading the generation of overdose ROS and oxidative stress [31,145,147]. Another mechanism involves the disruption of redox-sensitive systems by CBNs, which inhibits antioxidant enzymes and subsequently leads to ROS generation [149]. In some specific scenarios, intracellular ROS could also be induced by the CBN-drug composite system. For example, CBNs conjugated with drugs, such as doxorubicin and curcumin (common chemotherapeutic agents), have been shown to enhance ROS generation in cancer cells, alleviating symptoms [151,152].

4.2. Advanced approaches for modulating ROS generation

Modulating ROS generation by CBNs is crucial for optimizing their therapeutic potential while minimizing toxicity. Since CBNs primarily consist of carbon backbones, with predominantly sp^2 hybridized orbitals, various strategies have been developed to modulate their ROS generation properties without altering their core structure. These strategies include the introduction or alteration of their side groups, heteroatom doping, manipulation of their surface defects, and the formation of composites with other nanomaterials. These advanced approaches aim to fine-tune ROS generation capability of CBNs, enhancing their efficacy for therapeutic applications such as cancer treatment as well as their utilization as an anti-infection solution while maintaining their cellular redox balances.

4.2.1. Introduction or alteration of specific side groups

Main functional groups that can be easily introduced to the side/edge of CBNs include oxygen-containing groups (-C=O, -COOH, -OH), and nitrogen-containing groups (-NH_2/-NH) [29,127]. The -C=O group, for instance, has shown efficacy to catalyze the conversion of H_2O_2 into highly reactive $OH^{\bullet}$, as observed in CNTs and CQDs [29,98,114]. Additionally, it has been demonstrated that eliminating the -C=O from GQDs resulted in the most significant decrease in ROS generation, compared to the removal of -COOH and -OH groups [44,103]. Likewise, eliminating -C=O from oxidized g-C_3N_4 dramatically reduced the generation of $^1O_2$ [131]. These phenomena indicated the critical role of -C=O groups in CBN-mediated ROS generation, which can be due to their ability to promote spin–orbit coupling, narrowing down the singlet–triplet energy gap, thereby facilitating ROS generation [131]. However, the exact role of the -C=O groups during this catalysis remains elusive. In contrast to -C=O, -COOH groups can act as substrate binding sites for the GQD-mediated ROS generation reaction, promoting absorption onto the surface of CBNs [44,98]. Conversely, -OH groups inhibit substrate binding and hinder the catalytic reactions [103]. On the other hand, -NH_2 and -NH groups, known for their strong electron-donating properties, can be functionalized onto CBNs such as GQDs. This functionalization reduces the gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), thus increasing the efficiency of ROS generation [127]. Several other groups can also be functionalized onto the edges of CBNs through conventional bioconjugation chemistry [104,116,118]. For example, Jacquemin *et al.* showed that covalently attaching Diels-Alder derivatives, such as the reaction between the furan ring and various maleimides, to small GO sheets could enhance ROS generation when exposed to near-infrared (NIR) light, which is useful for cancer therapy [116].

4.2.2. Heteroatom doping

Doping of non-metal atoms, such as nitrogen (N) [155,156], phosphorus (P) [105], chlorine (Cl) [157], and sulfur (S) [158], is a prevalent strategy to modulate ROS generation in CBNs. Due to the significant electronegativity difference between these atoms and carbon, their introduction can enhance electron delocalization, thereby reducing the band gap energy between the HOMO and LUMO [128,130,154]. Meanwhile, careful consideration of the doping location is crucial, as it can significantly influence the electronic structure of CBNs and their resulting ROS-generating efficiency. For instance, N-doping can occur on different sites, such as graphitic-N, pyridinic-N, pyrrolic-N, and edge-NH_2. Graphitic-N usually reduces the band gap, while pyridinic-N and pyrrolic-N tend to increase it, likely due to differences in O_2 adsorption energy [114]. The non-metal doping also regulates indirect pathways of CBN-mediated ROS generation via cell-material interactions. For example, Deng *et al.* showed that N-doping suppressed a series of antioxidant enzymes in zebrafish, resulting in excessive ROS generation and accumulation. [149]. Additionally, Xiao *et al.* also showed that S-doping influenced the activity of SOD, leading to the over-production of ROS and lipid peroxidation in aquatic organisms [159].

Metal doping offers another effective way to enhance CBN-mediated ROS generation. Metals, with their larger atomic radii and numerous unoccupied orbitals, improve conductivity and decrease the HOMO-LUMO gap [128]. In this context, it is worth noting that specific metals can impart additional functionalities. For example, iron (Fe)-doping has been shown to enhance POD-enzyme-like properties, catalyzing the $OH^{\bullet}$ generation [100]. Manganese (Mn)-doping, meanwhile, can significantly enhance the generation of $^1O_2$ and $OH^{\bullet}$, while also serving as a contrast agent for magnetic resonance imaging (MRI) [121].

4.2.3. Surface defect manipulation and composite formation with other nanomaterials

The intrinsic interfacial properties of a material's surface, along with the presence of defects, give the surface distinct characteristics compared to the homogenous bulk. Atoms or molecules at the surface are less coordinated, leading to higher reactivity. Defects like vacancies further influence the material properties. During the photocatalytic reaction, effective defects on the surface can facilitate the trapping of the separated electrons and holes in distinct regions, increasing their ROS generation efficiency [29,99,132]. For instance, He *et al.* developed methods to create multiple nitrogen vacancies on the Fe-anchored g-C_3N_4 [137]. These vacancies acted as electron traps, preventing the recombination of electron-hole pairs and thereby improving the effectiveness of tumor sonodynamic therapy. Similar behavior was also observed in anti-pathogenic applications, where the $O_2^{\bullet-}$ and H_2O_2 generation increased by 4.6 times in the presence of nitrogen defects [133].

Additionally, to enhance the photocatalytic properties of CBNs, other

nanomaterials such as conventional semiconductors, including titanium dioxide (TiO_2) [160,161], molybdenum sulfide (MoS_2) [106,140], and zinc oxide (ZnO) [128,145], can be introduced to form CBNs/semiconductor composites, for more efficient electron-hole pairs separation, enhancing their ROS generation efficiency. In addition, metal nanomaterials have been also used to make a composite with CBNs for enhanced ROS generation because of the intrinsic superior conductivity of metal [128]. For instance, Panda *et al.* showed that GO-metal composites (with Fe, Ni, Zn, Sn) generated significantly increased ROS levels inside bacteria compared to GO alone, likely due to metal-enhanced nonoxidative electron transfer and greater disruption of the respiratory pathway [147].

4.3. Therapeutic applications of CBN-Mediated ROS generation

In recent years, CBN-mediated ROS generation has emerged as a powerful tool in modern medicine, offering innovative approaches for targeted therapeutic applications such as cancer treatment, infection control, and regenerative medicine [117,118,121,127,162]. This section explores the diverse therapeutic applications of CBN-mediated ROS generation, focusing on innovative strategies and their potential in various disease areas, including cancer therapy, antimicrobial treatments, and other emerging applications.

4.3.1. Cancer therapy

ROS-induced cancer treatment is one of the effective approaches in cancer therapy, as the tumor cells are more sensitive to the exogenous ROS compared to normal cells, likely due to differences in their antioxidant systems. PDT as one of the well-known therapies, relying on ROS-induced cancer disruption, was first introduced in the 19th century. Later, it gained renewed attention in the late 20th century and this resurgence led to the approval of the first PDT drug in the 1970s [117]. Despite its clinical success, PDT faces several challenges including limited tissue penetration, low targeting specificity, and its dependency on light activation.

To address some of these difficulties, nanomaterials such as CBNs offer potential solutions. As discussed earlier, by tuning their structure, such as functional groups, doping atoms, and surface defects, the ROS generation ability of CBNs could be tuned, expanding their application for cancer therapy [121,151,163]. Moreover, fine-tuning of CBN structures enables non-invasive, external stimuli-responsive activation (e.g., deep penetrating NIR and ultrasound) of ROS generation, which can in turn enhance anti-tumor activity [105,122,138,163]. For instance, adjusting the π-delocalized structure of CNT-based nanomaterials can modify their light absorption spectrum, enabling stimulation with NIR light. This approach was utilized in a mouse breast carcinoma model, where NIR-induced PDT effectively inhibited cancer progression without requiring invasive treatment [163]. Additionally, targeted delivery can be achieved by conjugating tumor-specific or tissue-specific molecules to CBNs, enabling precise delivery into tumor cells [139,150,153,164]. For instance, Ji *et al.* conjugated a DNA aptamer, known as the tumor cells recognizing ligand, to the CNDs for targeting the intracellular generation of ROS [123]. The aptamer on CNDs' surface could recognize the specific receptors on the membrane of tumor cells to assist the nanoparticles entering the cells. Under the catalytic effects of these CND-based nanoparticles, ROS could be successfully induced to kill the tumor cells. A similar strategy can be also used to target the activated vascular endothelial cells in tumor microenvironments. Fuidan, as a natural polysaccharide, is known to be a targeting ligand for P-selectin, highly expressed on the membrane of activated vascular endothelial cells [165]. Song *et al.* coated fucoidan on the CD-based nanoparticles to assist their anchoring on vascular endothelial cells, avoiding the clearance mediated by blood flow [124]. With the induction of NIR, the nanoparticles could generate ROS in the tumor microenvironment and inhibit the growth of tumor cells. Generally, the overall toxicity of CBNs for cancer therapy can be lowered and their therapeutic effects can be enhanced in the presence of tumor targeting ligands. Furthermore, given that different CBNs exhibit distinct wave absorption and ROS induction properties, it may be possible to enhance the therapeutic effects of CBN-based ROS-inducing therapy by selecting specific types of CBNs and utilizing external waves as a controller to finely tune *in situ* photochemical reactions. [105,135]. For example, Wang *et al.* developed a composite material based on phosphorus-doped carbon nitride (P-C_3N_4) and GQDs for catalytic therapy [105]. In this system, GQDs absorbed NIR light and transferred it into visible light within tissues. The visible light was then absorbed by P-C_3N_4, which catalyzed glucose to produce H_2O_2. Finally, GQDs acted as POD mimics to convert H_2O_2 into highly reactive $OH^{\bullet}$, which induced cancer cell apoptosis and necrosis (Fig. 5**a-i**). *In vivo* studies using a 4T1 tumor-bearing model showed that the P-C_3N_4/GQDs composites could significantly inhibit the tumor growth compared to pristine P-C_3N_4 or GQDs, with almost 90 % reduction in tumor volume and weight compared to the individual components (Fig. 5**a-ii**). Additionally, in recent years, a deeper understanding of the tumor microenvironment has boosted the development of environment-responsive drug delivery systems. One notable hallmark of the tumor microenvironment is elevated levels of ROS, making ROS responsiveness a promising strategy for dynamic cancer therapy using CBNs. For example, in targeting colorectal cancer (CRC), Xu *et al.* developed a system in which CDs-loaded lipid nanoparticles were conjugated to the surface of *Limosilactobacillus reuteri* (LR), a probiotic bacterium, via ROS-responsive thioether bonds [125]. Upon oral administration, the nanoparticles could concentrate in the ROS-enriched tumor microenvironment, where elevated ROS levels triggered the cleavage of the thioether linkers, thereby releasing the CDs-loaded nanoparticles from the bacterial carriers. This tumor-specific release was facilitated by the ROS-responsive nature of the linkage. Then, the subsequent NIR irradiation could trigger a sharp increase in cytotoxic ROS, leading to effective tumor cell damage.

In summary, various strategies have been developed for utilizing CBNs to overcome the challenges associated with PDT for cancer treatment. While CBN-based cancer therapy offers advantages such as high specificity, low invasiveness, and precise control of dynamic reactions, there are still some shortcomings that need to be considered. For example, the fabrication and *in vivo* application of these nanomaterials remain complex, particularly when all the above-mentioned properties (high specificity, low invasiveness, and precise control) must be simultaneously achieved within a single therapeutic scenario. To address these challenges, further efforts are required to simplify and optimize the fabrication, modification, and functionalization processes of CBNs for cancer therapy. Moreover, advancements in cancer biology could serve as a valuable source of inspiration to enhance the specificity and therapeutic efficacy of CBNs in tumor microenvironment, minimizing off-target effects and preventing damage to healthy cells.

4.3.2. Infection treatment

The emergence of antibiotic-resistant bacterial infections, coupled with the limited availability of effective treatments for fungal infections, highlights the critical need for developing novel therapeutic strategies [107,166]. In this regard, by leveraging the robust ROS generation capabilities, CBNs can present an alternative treatment option. At the infection sites, ROS can act as a potent agent, disrupting microbial structure and metabolism [167,168]. In this context, CBNs can produce ROS either by itself to kill microbes, or can locally boost ROS production. This dual action makes CBNs a powerful tool for treating infections. For example, Dai *et al.* fabricated defect-rich g-C_3N_4 QDs with POD-like activity [108]. They demonstrated that the QDs could directly enter into the microorganisms, such as *E. coli* (Gram-negative), *S. aureus*, *B. subtilis* (Gram-positive), and *R. solani* (fungi), generating $OH^{\bullet}$ radicals to effectively kill microbes through ROS. However, this study was only limited to *in vitro* assessment without any *in vivo* efficacy evaluation. Additionally, the efficacy of the QDs nanozyme was not manually controllable, raising concerns about its potential toxicity to healthy

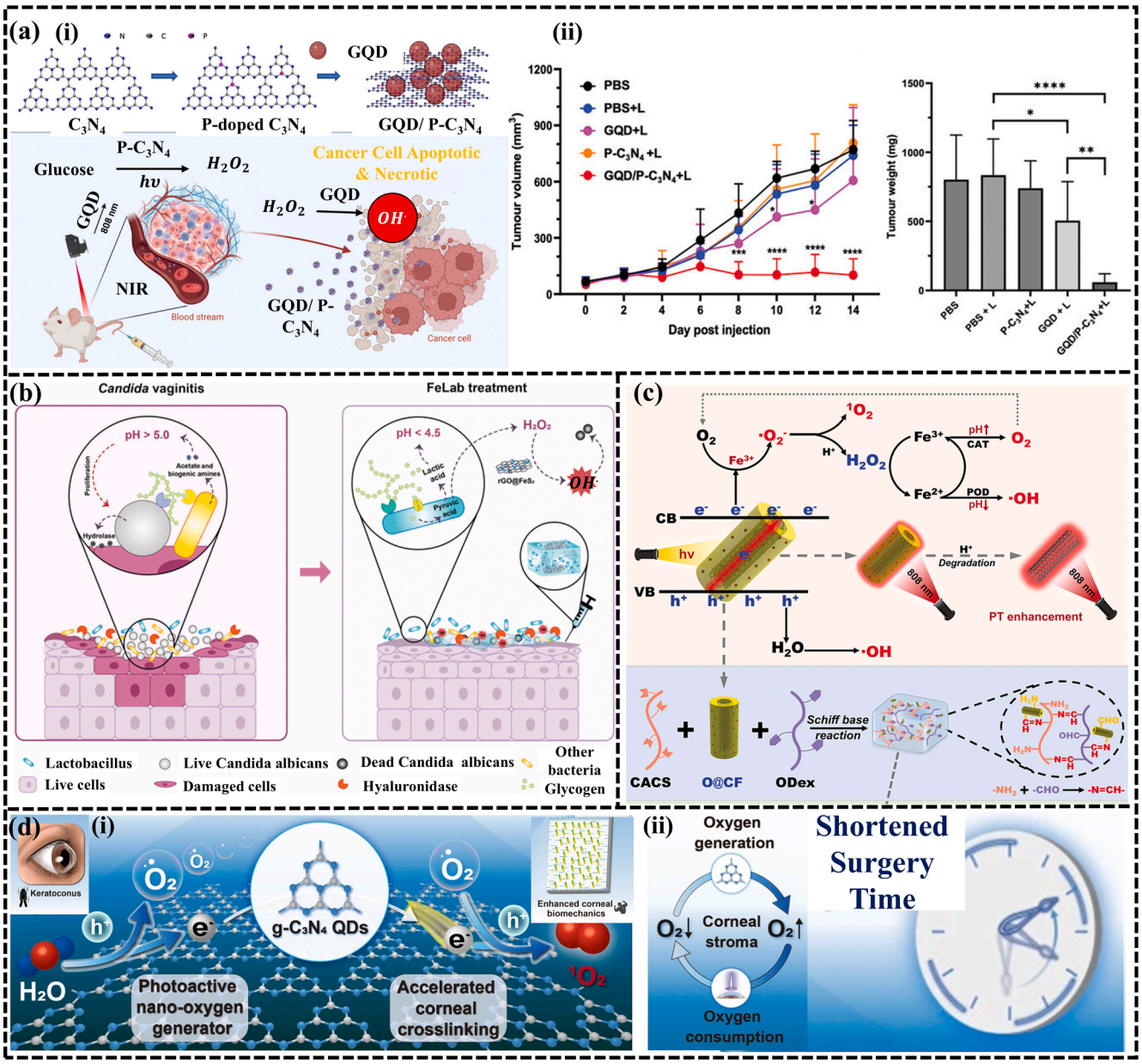

Fig. 5. Applications of CBN-mediated ROS generation in medicine. (a) Combining different CBNs for tumor therapy: (i) Development of phosphorus-doped graphitic carbon nitride (P-C_3N_4) and graphene quantum dots (GQDs) composite inducing series catalytic reactions for cancer cells killing. Under the catalyzing effects of P-C_3N_4, glucose can be transferred to hydrogen peroxide (H_2O_2) after which the GQDs can catalyze H_2O_2 to form hydroxyl radicals ($OH^•$); (ii) Tumor weight and volume after materials' injection showing that treatment group combining GQDs and P-C3N4 had significantly lower tumor volume and weight compared to the groups (single CBN alone). Reproduced with permission from [105] Copyright 2024, John Wiley & Sons. **(b)** Reduced graphene oxide (rGO)/FeS_2 (rGO@FeS_2) nanozyme to engineer composite hydrogels for vaginitis treatment. Reproduced with permission from [101] Copyright 2023, American Association for the Advancement of Science. **(c)** Incorporation of modified carbon nanotubes (CNTs) in a Schiff-based hydrogel for antibacterial applications in infected diabetic wounds management. Reproduced with permission from [113] Copyright 2024, John Wiley & Sons. **(d)** Development of a g-C_3N_4-based platform to reduce surgery time for keratoconus treatment: (i) Self-oxygen-supplied g-C_3N_4 to enhance UV crosslinking of the cornea; (ii) reduction of surgery time due to oxygen molecules recycling. Reproduced with permission from [134] Copyright 2024, Springer Nature.

tissues. In another work, He *et al.* developed celery-based CDs with light-controlled nanozyme efficacy, possessing POD-like activity under light irradiation [126]. These CDs exhibited excellent therapeutic effects in promoting infected wound healing and killing gram-positive bacteria in wounds. In addition, for treating deep tissue infections, such as chronic osteomyelitis and deep wounds, researchers have explored the use of tissue-penetrating waves, such as microwaves and NIR light, to induce ROS generation, effectively bypassing tissue barriers [100,140,154].

On the other hand, CBNs such as GO/rGO, with their unique geometric shape and nanoscale dimensions, can disrupt bacterial lipid bilayers and trigger intracellular ROS generation [31,96,154]. Additionally, the contact between microbes and CBNs with specific surface charges can also induce ROS in microbes, exerting antimicrobial effects. For example, Chen *et al.* synthesized biophilic positively charged CDs for fungal keratitis treatment [107]. Fungal spores treated with CDs exhibited significantly higher levels of intracellular ROS compared to untreated groups. Furthermore, CBNs can interfere with the electron transfer process on bacterial membranes, leading to the accumulation of ROS inside the bacteria and ultimately causing cell death. While the interaction of CBNs with microbial structures and metabolism

effectively deactivates bacteria, it may suffer from low specificity and limited control, potentially leading to unintended ROS generation in healthy cells [146,148].

Another challenge in using CBNs for infection treatment is achieving the optimal dosage at infection sites in real-world applications. Direct application of CBNs often results in low bioavailability due to rapid clearance by body fluid flow. Conversely, increasing the dosage or forming nanoaggregates for localized applications may lead to toxicity in normal cells and tissues [169]. To overcome these challenges, a notable trend in this field involves incorporating ROS-generating CBNs into bulk biomaterials, such as hydrogels, to control dosage and reduce clearance [101,106,113,118]. Hydrogels, with their high water-content, tissue-like mechanical properties, and excellent tissue integration capability, serve as ideal matrices for ROS-generating CBNs, enhancing their efficacy [170,171]. For example, Wei *et al.* incorporated rGO@FeS_2 and probiotics *Lactobacillus* into a hyaluronic acid hydrogel to treat Candida vaginitis, a common fungi infection affecting vaginal area (Fig. 5**b**) [101]. The engineered hydrogel created a favorable environment for probiotics (*Lactobacillus*) to survive and grow, leading to the generation of H_2O_2. Under these conditions, rGO@FeS_2, acting as a POD-like nanozyme, catalyzed the decomposition of H_2O_2 into $OH^{\bullet}$ radicals, which effectively killed *Candida albicans*, a common pathogen responsible for Candida vaginitis. It is worthwhile to mention that in this case, rGO@FeS_2 was effectively protected from local clearance in the vagina with the assistance of hydrogel encapsulation, allowing them to play a crucial role in the biochemical reaction chain for the continuous production of toxic $OH^{\bullet}$. In another study, Lin *et al.* incorporated CNTs-based nanorods into a Schiff-based hydrogel (Fig. 5**c**) [113]. The fabricated hydrogel could effectively adhere to wound surfaces and serve as a matrix for transmitting NIR/yellow light. Upon light activation, the nanocomposites initiated a series of photochemical reactions, converting O_2 into $OH^{\bullet}$, which significantly killed both Gram-positive and Gram-negative bacteria. Thus, this process promoted rapid healing of infected diabetic wounds.

In summary, ROS generation mediated by CBNs, through both direct and indirect pathways, has shown great promise in combating bacterial and fungal infections across various applications. On the other hand, incorporating CBNs into bulk materials like hydrogels can enhance the antimicrobial efficacy of ROS generation by providing better control over dosage as well as improving interfacial properties. Despite their potential, challenges remain, such as ensuring precise control over ROS generation, avoiding toxicity to healthy cells, and optimizing *in vivo* efficacy. Researchers should focus on addressing these limitations by developing more targeted delivery systems, improving the specificity of CBN interactions with microbes, and exploring new approaches to fine-tune ROS production in clinical settings.

4.3.3. Other applications

Excessive ROS generation by CBNs not only aids in cancer therapy and infection treatment but also demonstrates significant potential in addressing a variety of emerging therapeutic challenges, where their unique properties can be leveraged for complex medical conditions. For example, Yang *et al.* utilized self-oxygen-supplied g-C_3N_4 for photocatalytic reactions within the cornea to accelerate UV-crosslinking in the treatment of keratoconus (Fig. 5**d-i**) [134]. When exposed to light, CBNs generated electron-hole pairs, triggering both Type I and Type II reactions that produce excessive ROS in the corneal tissue, thereby promoting crosslinking. This process significantly shortened the surgery time from approximately 1 h to just 10 minutes, reducing the prolonged UV exposure to healthy eye tissues (Fig. 5**d-ii**). This approach enhanced treatment efficiency and improved patient compliance. Additionally, elevated ROS levels can also be used to modulate immune response for vaccine applications. In this context, Xu *et al.* conjugated tumor mutations-derived neoantigens to the rGO nanoparticles and delivered them to the lymph nodes [150]. By inducing intracellular ROS generation in dendritic cells through the interactions between the rGO and the cell membrane, the antigens could be processed. This, in turn, elicited antigen-specific T-cell responses to combat tumor cell progression.

In the future, ROS-generating CBNs hold the potential to expand to other applications in the biomedical field, such as wound healing and immunomodulation. For example, polymers with acrylate group in the side chain, such as gelatin methacryloyl (GelMA) and poly (ethylene glycol) diacrylate (PEGDA), usually undergo free radical crosslinking to form crosslinked hydrogels in the presence of photoinitiators and light radiation [172]. Then, the crosslinked hydrogels can be used for wound dressings. However, the hydrogel crosslinking density and mechanical properties remain the same for the whole wound healing process, which presents a lack of dynamic mechanical trigger to maintain the wound contractibility and gradually promote wound closure [173]. In this case, the addition of CBNs to these polymeric hydrogels can induce ROS responding to the changes in the wound microenvironment. ROS themselves also act as free radicals, aiding in the secondary crosslinking, improving the mechanical properties of the hydrogel and its ability to close the wounds. Moreover, ROS can be leveraged for immunomodulation, stimulating immune responses to combat pathogens, including microbes and tumor cells. This approach offers the advantage of reducing toxicity to normal cells, a common concern in dynamic therapy [174]. These diverse applications underscore the expanding role of ROS-generating CBNs beyond their current therapeutic uses, paving the way for broader clinical adoption.

5. Harnessing CBNs for ROS scavenging, modulation and their applications

Leveraging their unique properties, CBNs can function dually by either amplifying or mitigating ROS levels based on specific therapeutic requirements. This dual functionality enables CBNs to act as effective regulators of redox balance, opening promising applications in immunomodulation, tissue repair, and the treatment of conditions related to oxidative stress. Building on the understanding of ROS generation mechanisms induced by CBNs, it is essential to explore the broader potential of these nanomaterials in controlling ROS levels. While the previous section emphasized ROS generation as a therapeutic strategy, this section will shift the focus to the role of CBNs in ROS scavenging and modulation. We will conduct a comprehensive exploration of the mechanisms, modulation strategies, and applications of CBNs in ROS scavenging (Fig. 6). The related information is summarized in Table 2.

Unlike ROS generation by CBNs, which typically depends on external triggers like NIR or ultrasound, certain CBNs possess an inherent ability to scavenge ROS without the need for external activation. This capability is influenced by fabrication techniques and employed modulation strategies, highlighting the versatility of CBNs in regulating redox balance. Thus, CBNs hold potential as next-generation antioxidant agents while some derivations, such as fullerenes and CDs, exhibit superior antioxidant capabilities compared to conventional agents including phenol [114,210]. In addition, CDs can interact with cells to boost intracellular metabolism and promote ROS scavenging [200,201]. In recent years, research on ROS-scavenging CDs has gained significant momentum, driven by their easy fabrication processes, exceptional biocompatibility, and outstanding radical scavenging performance [114,128,211]. In addition, there are several studies on the ROS-scavenging efficacy of other CBNs, including fullerenes and their derivatives [26,210,212–214], CNTs [188], and GO [25,188,189,215].

5.1. Mechanistic pathways of ROS scavenging by CBNs

The mechanisms by which CBNs scavenge ROS can be broadly classified into enzymatic and non-enzymatic pathways. Enzymatic scavenging involves mimicking the catalytic functions of natural enzymes such as SOD and CAT. Non-enzymatic mechanisms, on the other hand, can further be divided into five distinct subcategories: (a) hydrogen donation/transfer; (b) electron transfer; (c) radical adduct

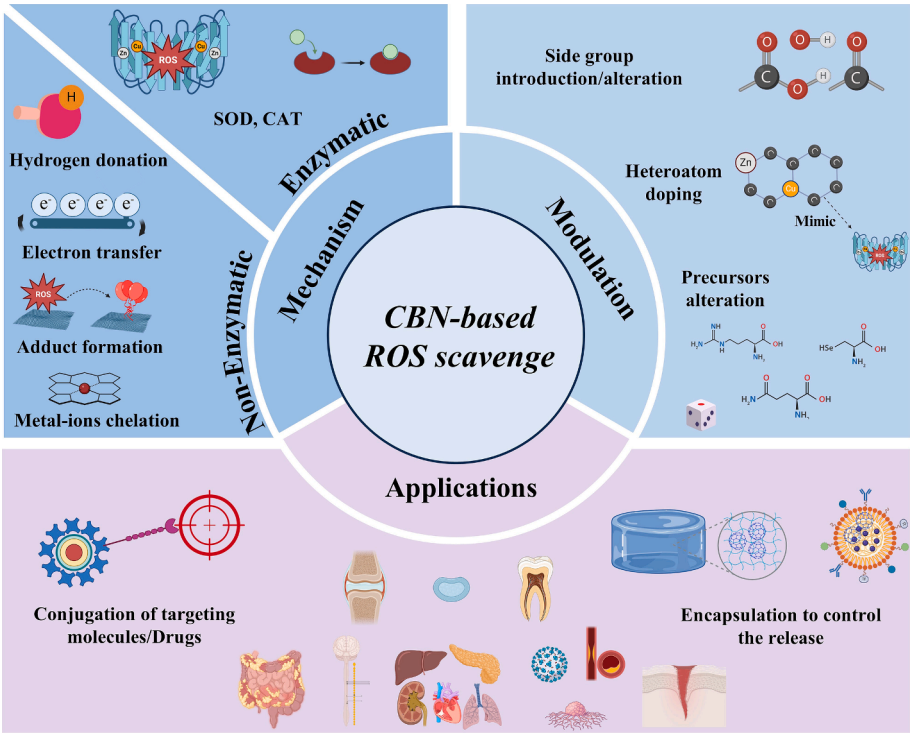

Fig. 6. Mechanisms, modulation strategies, and advanced applications of CBN-mediated ROS scavenging [Generated from Biorender].

Table 2
Summary of CBN-based ROS scavenging strategies.

Mechanisms		Modulations	Nanomaterial types	Applications	References
Enzymatic	SOD	Precursors alteration, heteroatom doping	CDs, fullerenes, carbon cluster	Inflammation control (Liver, gastrointestinal tract, lung), intervertebral disc degeneration	[27,28,175,176,177,178,179,180,181,182,183,184,185]
	CAT	Precursors alteration, heteroatom doping	CDs	Intervertebral disc degeneration, bone infection, neurotoxicity	[175,178,179,180,185,186,187]
Nonenzymatic	Hydrogen donation	Side group introduction/ alteration	CDs, fullerenes derivatives, CNTs	Wound healing, cardiac repair, inflammation (Pulmonary, neuronal), Parkinson's disease	[26,114,187,188,189,190,191,192,193,194,195,196,197,198,199]
	Electron transfer	Side group introduction/ alteration, heteroatom doping	CDs, fullerenes derivatives, CNTs		
	Adduct formation	Side group introduction/ alteration, precursors alteration	Graphene/GO, fullerene derivatives, CDs, CNTs		
	Metal-ions chelation	Side group introduction/ alteration, precursors alteration	Graphene/GO, CDs	Acute lung injury, Parkinson's disease	[176,189,193]
	Metabolism manipulation	Precursors alteration, heteroatom doping	CDs, GO	Colitis, Parkinson's disease, bone infection, kidney injury	[200,201,202,203,204,205,206,207,208,209]

formation; (d) transitional metal ions chelation; (e) material-cell interactions.

5.1.1. *Enzymatic ROS scavenging*

Enzymatic scavenging refers to the process by which CBNs mimic the catalytic functions of natural enzymes, such as SOD and CAT, to efficiently scavenge ROS through redox reactions.

The natural enzymes like SOD catalyzes the conversion of $O_2^{\bullet-}$ into H_2O_2. While CAT could break down H_2O_2 into H_2O and O_2. In this context, certain CBNs, particularly CDs, display SOD- or CAT- like cat-

alytic properties, allowing them to efficiently scavenge ROS [27,28,175–179,186,187,201]. Besides CDs, fullerenes [180], and some specially prepared CBNs [181] also exhibit SOD-like properties. For example, Samuel *et al.* reported that their synthesized hydrophilic carbon cluster exhibited SOD-like catalytic behavior, following Michaelis Menten saturation kinetics as the concentration of substrate ($O_2^{\bullet-}$) gradually increased [181]. They also proposed a straightforward two-step reaction mechanism to explain the catalytic process. Interestingly, the carbon cluster demonstrated selectivity by remaining inert to other radicals, such as reactive nitrogen species, mirroring the substrate specificity observed in natural enzymes.

5.1.2. Non-enzymatic ROS scavenging

Non-enzymatic ROS scavenging by CBNs involves direct electron transfer and hydrogen atom donation from the functional groups on their surface, enabling the neutralization of ROS without the need for enzymatic catalysis. In this regard, hydrogen donation is a commonly proposed mechanism to explain the radical scavenging efficacy of CBNs [211], particularly those with a significant number of functional groups, such as GQDs [190], fullerenes [191], and GO [192]. This mechanism is especially effective in scavenging radicals like 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) [114,189–191,211]. In this process, functional groups such as -OH, -COOH, and -NH/-NH_2 can directly donate hydrogen atoms to these radicals, while the instability caused by unpaired electrons on these groups is stabilized by the delocalized electrons in the sp^2-hybridized carbon frameworks of CBNs [192]. Another CBN-mediated ROS scavenging mechanism is electron donation [211]. It originates from the abundance of delocalized electrons in the carbon network, allowing CBNs to donate electrons to adjacent radicals and thereby scavenge ROS. Historically, researchers have used donor–acceptor maps or computational methods to evaluate the effectiveness of specific molecules, such as certain phenols, as electron donors [114]. However, these methods are less applicable to nanomaterials like CBNs due to their complex structure, which includes the backbone, functional groups, heteroatoms, and defects. Therefore, the electron-donating capability of CBNs should be estimated by considering factors such as the ratio of sp^2/sp^3 hybridization, the presence of side groups, the electronegativity of heteroatoms, and the distribution of structural defects.

Radical adduct formation [189], another non-enzymatic pathway to scavenge ROS, refers to the formation of a complex between CBNs and radical/ROS. Secondary adducts often form around sp^2-rich carbon sites [189]. It is important to note that this mechanism typically relies on support from the other two mechanisms (hydrogen donation/transfer and electron transfer). For example, CNTs and GQDs often scavenge ROS by both electron transfer and radical adduct formation [192]. Similarly, in the case of fullerenes derivatives scavenging DPPH, second adducts commonly form following hydrogen donation [191]. Chelation of transition metal ions, such as Fe, is also another important mechanism for scavenging ROS. In this case, a POD-like or Fenton-like reaction can boost the formation of acutely toxic $OH^{\bullet}$, with transition metal ions serving as efficient catalysts. Instead of relying on doping to enhance ROS generation, this mechanism utilizes the electron-rich side groups of CBNs to chelate metal ions, thereby inhibiting ROS-generating reactions within cells [176,189,193]. As a result, the formation of $OH^{\bullet}$ is reduced, effectively alleviating oxidative stress. In addition, some CBNs like CQDs [200,201] and normal GQDs [202,203] can regulate ROS levels by modulating cell metabolism or influencing redox-sensitive pathways. By interacting with cells, these materials can upregulate the production of antioxidant enzymes such as SOD or CAT, thereby enhancing ROS scavenging ability.

5.2. Strategies for modulating ROS-scavenging ability of CBNs

Similar to modulating ROS generation, the ROS scavenging properties of CBNs can be tailored through the introduction or alteration of specific side groups and heteroatom doping. Additionally, modifying precursors can further enhance the antioxidant properties of certain CBNs. These advanced approaches aim to fine-tune ROS scavenging, thereby enhancing the efficacy of CBNs in a variety of applications, including the treatment of colon disorders, wound healing, nervous system diseases, and many more.

5.2.1. Introduction or alteration of specific side groups

In the context of modulating ROS scavenging by CBNs, the introduction or alteration of specific side groups can be an effective strategy. For example, the ROS scavenging ability of fullerenes is strongly influenced by their surface functional groups [26,216]. Pure fullerenes exhibit almost no scavenging ability because of their poor solubility in solution, and their tendency to aggregate [194,212]. Whereas the surface functionalization of fullerenes with hydrophilic groups, such as -OH or -COOH, can significantly improve their ROS-scavenging properties [195]. Notably, -OH group functionalization has demonstrated greater effectiveness compared to -COOH group functionalization, making fullerenol (–OH functionalized fullerenes) a widely studied material [26]. This effect may be attributed to the significant increase in the electron affinity of fullerenes upon the introduction of -OH groups. Additionally, introducing -OH groups can modify the surface of fullerenes, creating electron-deficient regions that facilitate the binding of $O_2^{\bullet-}$, enabling SOD-like catalytic activity. Another contributing factor could be that the introduction of the -OH groups reduces aggregation, thereby increasing the available surface area for radical binding [26]. CNTs also exhibit a similar dependency on surface functionalization for their ROS-scavenging properties [188]. In contrast, for CQDs, alteration of the functional groups could affect both enzymatic and non-enzymatic ROS-scavenging properties. In the context of non-enzymatic scavenging, modifications to functional groups such as -OH, -COOH, or -NH_2 can significantly influence hydrogen transfer capabilities. For example, GQDs with fewer functional groups and more sp^2 sites exhibit strong $OH^{\bullet}$ scavenging but weaker DPPH scavenging, as DPPH elimination closely relies on hydrogen transfer, whereas $OH^{\bullet}$ scavenge usually occurs at sp^2 sites [192]. Conversely, for enzymatic scavenging, catalytic activity mainly relies on the precise interplay of functional groups and the structural framework of the materials. In SOD-like catalysis of $O_2^{\bullet-}$, the -OH and -COOH groups facilitate substrate ($O_2^{\bullet-}$) binding. Simultaneously, the -C=O conjugated with the π-electron system functions as catalytic sites, enabling efficient electron transfer to drive the reaction. [27,44,176,179].

5.2.2. Heteroatom doping and other modulation approaches

Beyond side group modifications, non-metal doping, particularly N doping, has been widely recognized as an effective strategy to enhance the luminescence properties of some specific CBNs, such as CDs [176,217]. Additionally, it has been demonstrated that non-metal doping can enhance the catalytic performance of ROS scavenging by redistributing charge and spin, thereby increasing the availability of active sites on carbon atoms for enhanced catalysis [158,218,219]. On the other hand, doping with specific metal ions offers an effective alternative for enhancing ROS-scavenging properties. Doping of metals like cerium (Ce), gadolinium (Gd), copper (Cu), and zinc (Zn) can confer SOD- or CAT-like catalytic properties to CBNs like fullerenes and CDs, significantly boosting their ROS-scavenging abilities [26,187,219,220]. Beyond enzymatic activity enhancement, metal doping also improves electron transfer for non-enzymatic ROS scavenging due to the excellent conductivity of metals [187]. For instance, Se doping is noteworthy due to its crucial role in intracellular antioxidant cascades. In recent years, Se-doped CQDs have been extensively used in biomedical applications to regulate redox-sensitive systems [204–207].

Side group alteration and doping of heteroatoms are two main approaches for CBN-mediated ROS scavenging modulation. However, for CBNs such as CQDs, which are fabricated via a simple bottom-up

hydrothermal approach, selecting and modifying molecular precursors provides an efficient strategy for modulation [175,178,201,208]. For example, single molecules such as *N*-acetylcysteine [178], melatonin [208], glutathione [175], or arginine [201], which are crucial in redox-sensitive systems or immune regulation, can be utilized as starting materials. Thus, changing the reactants can lead to variations in functional groups, sp^2/sp^3 ratio, and heteroatom composition. Meanwhile, it is anticipated that using these molecules will enhance cell-material interactions, resulting in improved ROS scavenging properties.

5.3. Recent advances and emerging applications

As discussed in previous sections, the characteristics of CBNs can be fine-tuned for medical use, especially in maintaining and restoring redox homeostasis in physiological systems. Disturbances in intracellular redox balance across different tissues are often marked by a significant increase in intra- and extra-cellular ROS levels, contributing to disease progression. In this context, understanding of CBN-mediated ROS scavenging mechanisms and modulation techniques enables the utilization of CBNs as valuable therapeutic agents for targeted delivery and effective disease management. For example, in recent years, ROS-scavenging CBNs, especially fullerenes and CDs, have been extensively used to address inflammation and organ disorders. Applications span across multiple pathologic conditions, including colon disorders [177,182–184,202], wound healing [196,197,221], bone-related dysregulation [201,207,222], intervertebral disc degeneration (IVD) [178], dental application [175,185,208], nervous system disorders [186,193,203,223,224], and several hepatic [28,205,213,225], gastrointestinal [220], renal [206], cardiac [198,209], blood vessel [226] and pulmonary [176,227] diseases. Additionally, some researchers have also explored their efficacy in treating viral infections [228] and cancer [194].

In recent studies, two key approaches are shown for improving the therapeutic effects of ROS-scavenging CBNs. These include: i)

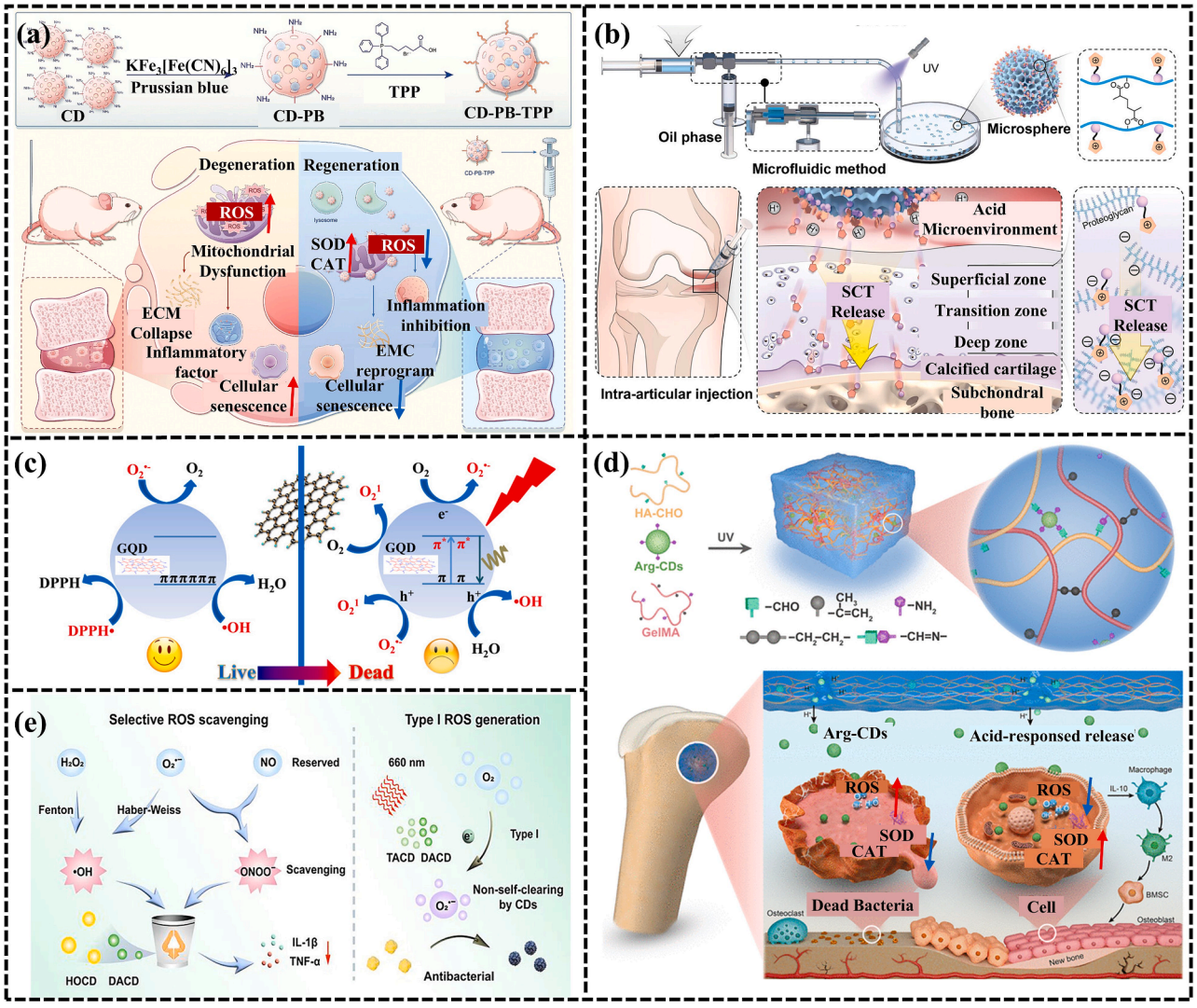

Fig. 7. Recent emerging applications in ROS scavenging and generation by CBNs: (a) Conjugation of lipophilic cations-triphenylphosphine (TPP) onto carbon dots (CDs) to target mitochondria membrane, scavenging newly generated ROS during IVD process. Reproduced with permission from [185] Copyright 2024, John Wiley & Sons. **(b)** Fabrication of selenium-doped carbon quantum dots (Se-CQDs) loaded micro/nano hyaluronic gel particles for prolonged release of Se-CQDs and scavenging deep tissue ROS for osteoarthritis treatment. Reproduced with permission from [207] Copyright 2024, John Wiley & Sons. **(c)** Light on/off switching of graphene quantum dots (GQDs)-based ROS generation/scavenging properties. Reproduced with permission from [237] Copyright 2016, American Chemical Society. **(d)** Development of arginine-derived carbon dots (Arg-CDs) loaded in hydrogels to generate ROS for bacterial killing, while simultaneously boosting antioxidant enzyme expression in healthy cells for treatment of infected bone injuries. Reproduced with permission from [201] Copyright 2023, American Association for the Advancement of Science. **(e)** Development of structurally oriented CDs to protect beneficial ROS, remove harmful ROS, and generate ROS for antibacterial purposes. Reproduced with permission from [238] Copyright 2024, American Chemical Society.

conjugation of targeting molecules and/or drugs to CBNs to enhance precision and efficiency, and ii) encapsulation of CBNs for controlled release. Typically, the ROS-scavenging effects of CBNs are not specific, potentially exposing healthy tissues to high doses. By attaching targeting molecules to CBNs, they can precisely locate and act on dysfunctional areas. For example, Wang *et al.* conjugated triple-functionalized human serum albumin (HSA-BFP) to CDs, targeting amyloid β-protein (Aβ), a marker for Alzheimer's disease, to deliver antioxidant therapy to affected regions [224]. Similarly, Shi *et al.* used triphenylphosphine (TPP), a mitochondrial-targeting ligand, to create CD-Prussian blue-TPP conjugate (CD-PB-TPP), which can avoid lysosomal phagocytosis and target the mitochondrial membrane to scavenge ROS (Fig. 7**a**) [185]. The nanodrug further showed effectiveness in reducing tissue senescence and inflammation in a rat IVD model. Other conjugations might involve commercial drugs or conventional antioxidants, such as dexamethasone (i.e., anti-inflammatory corticosteroid) conjugated with CQDs to reduce liver inflammation [225], or antioxidant molecules like lecithin and carnosine conjugated with CBNs like fullerenes and CQDs to enhance antioxidant properties [199,205].

Due to their small size (~5 nm), CBNs like CDs and fullerenol can be rapidly cleared by systemic circulation, resulting in low availability at target sites. Encapsulating CBNs within delivery vehicles can enable controlled release, extending their functional lifespan while enhancing biocompatibility and bioactivity. In this context, bulk materials, especially hydrogels, are ideal candidates as encapsulating matrices. For instance, alginate and gelatin-based hydrogels have been used to deliver fullerenol to modulate the local microenvironment for promoting cardiac repair [198], or skin wound healing [196]. Apart from conventional methods, recent advances in microfluidic techniques have also allowed the fabrication of hydrogels in micro- or nano-forms for applications in regenerative medicine [207,229]. For example, Zuo *et al.* utilized microfluidic techniques to create a hyaluronic acid-based hydrogel designed to encapsulate Se-doped CDs for sustained release in the knee joint during osteoarthritis treatment (Fig. 7**b**) [207]. Their findings further suggested that Se-CQDs effectively penetrated the cartilage tissue *in vivo* and, through downregulation of ROS, protected local tissues from matrix metalloproteinase 13 (MMP13) mediated degradation. Other nanoparticles such as liposomes [177,226], metal–organic frameworks [182], and chitosan [220] have also been used to encapsulate CDs and control their release. Additionally, CBNs have also been incorporated in ROS-responsive hydrogel for the controlled release to provide on-demand ROS scavenging properties. For example, Dai *et al.* incorporated the zinc-CDs (Zn/CDs) nanozymes in a hydrogel constructed by the ROS-responsive phenyl-boronic ester bond between polyvinyl alcohol (PVA) and phenylboronic acid functionalized hyaluronic acid (HA-PBA) for the therapy of diabetic wounds [230]. In this system, the presence of elevated ROS levels in the wound microenvironment triggered hydrogel degradation, leading to the release of Zn/CDs nanozymes. The released nanozymes then catalytically scavenged excess ROS, thereby alleviating oxidative stress. Besides, in ROS-responsive hydrogel, CBNs, such as rGO, could act as carriers for antioxidant drug delivery because of their large surface area of π-π conjugate system and abundant functional groups [222]. When incorporated into ROS-responsive matrices, these CBN-based drug delivery systems enabled stimuli-responsive release profiles, ensuring that antioxidant therapeutics were delivered in accordance with the local ROS levels. This approach offered a promising strategy for achieving spatiotemporal control of oxidative stress in pathological environments.

In conclusion, ROS scavenging by CBNs is emerging as a promising alternative to traditional antioxidants. By leveraging multiple approaches in the drug delivery, the specificity and bioavailability of CBNs can be optimized for advanced applications. In the future, several promising directions merit further investigation in the development of CBN-based ROS-scavenging systems. First, controlled release platforms specifically designed for ROS-scavenging CBNs, such as fullerene derivatives and CDs, remain relatively underexplored. Given the importance of dose-dependent effects, the use of environmentally sensitive linkers (e.g., ROS-, pH-, or enzyme-responsive) could provide precise control over release kinetics and enhance therapeutic efficacy. Furthermore, the abundant surface functional groups on CBNs offer a valuable opportunity for site-specific bioconjugation of responsive linkers, enabling targeted and on-demand ROS scavenging. Moreover, because of the accumulated oxidative stress in age-related degenerative diseases, such as Alzheimer's disease [231], age-related macular degeneration [232], glaucoma [233,234], and osteoarthritis [235,236], CBN-based ROS scavengers hold significant potential as alternative redox-regulating therapeutics. These platforms could play a critical role in mitigating oxidative damage and possibly reversing degenerative progression. The next section will explore the dual role of CBNs in ROS regulation (both the generation and scavenging properties) and the challenges of relying solely on ROS generation or scavenging for the management of complex diseases.

6. Maintain redox homeostasis by CBNs: promises and pitfalls

To maintain redox homeostasis in the human body, a balance between ROS generation and elimination is essential. This requires a dual-sided regulation strategy that leverages both generation and scavenging to ensure adequate ROS levels for physiological functions in real-world applications. To address this, various CBNs possess distinct properties for managing ROS, but a common trait among them is their dual capacity to both generate and scavenge ROS. For instance, fullerenes' ROS-regulating properties are closely linked to their hydrophilicity and aggregation tendencies. Hydrophilic and smaller fullerenes typically exhibit strong ROS-scavenging abilities, while hydrophobic and aggregated ones generally induce ROS. Furthermore, some fullerenes are light-sensitive, generating ROS when exposed to illumination [114]. In contrast, CNTs demonstrate more complex behaviors. MWCNTs demonstrate ROS-scavenging abilities in solutions, but their asbestos-like structure can trigger ROS production in tissues *in vitro* or *in vivo*, causing cellular or tissue damage [5,239,240]. SWCNTs, on the other hand, have shown mixed results. Some studies highlight ROS-scavenging properties of SWCNTs and their low toxicity [111,188], while others indicate their light-independent ROS generation even in solutions, leading to DNA damage [241]. These discrepancies are likely due to variations in their fabrication techniques and structural properties. Likewise, graphene and GO also exhibit controversial ROS-regulating properties. Some studies suggest ROS-dependent toxicity in graphene and GO compared to the smaller GQDs [148,242,243]. Conversely, there is evidence of antioxidant properties in GO, necessitating caution when designing graphene/GO-based materials for ROS regulation [189]. CDs, such as CQDs and GQDs, generally act as ROS scavengers in the absence of light but can generate ROS under specific light wavelengths. Side group alterations or heteroatom doping can be used to modulate the light-dependent ROS generation. For example, -C=O groups often serve as catalytic sites: promoting photocatalysis to boost ROS generation in the presence of light, while exhibiting SOD-like catalytic activity to scavenge ROS in darkness. One study by Yu *et al.* highlighted the dual antioxidant and pro-oxidant properties of GQDs under varying light conditions (Fig. 7**c**), showcasing their potential for disease-related ROS regulation [237].

In complex disease regulation, such as infections and cancer, simple ROS scavenging or generation is usually insufficient. This challenge arises from the coexistence of two distinct biological groups in the pathological environment: infecting bacteria/fungi or cancer cells, and normal cell populations. Inducing ROS can harm normal cells while scavenging ROS may inadvertently promote pathogen or cancer cell growth. Therefore, an efficient strategy to achieve dual management of ROS is critical. In recent years, significant progress has been made to address this issue. For example, Li *et al.* developed an arginine-derived CDs (Arg-CDs) encapsulated in a Schiff-based hydrogel, for controlled release in response to pH changes in an infected bone injury

microenvironment (Fig. 7**d**) [201]. These Arg-CDs induced ROS to kill bacteria while upregulating SOD/CAT expression in adjacent normal cells, thereby protecting them. Additionally, Arg-CDs did not alter the expression of antioxidant enzymes in bacteria, effectively eliminating infection while safeguarding normal tissues from ROS-induced damage. Similarly, Se-doped GO was also designed to effectively scavenge ROS under high-ROS conditions and generate ROS when intracellular ROS levels are low. However, the precise mechanism driving these dual functions is not well understood, and its applicability to divergent cell populations requires further exploration [104]. Additionally, some researchers have emphasized the role of certain ROS, such as H_2O_2 and $O_2^{\bullet-}$, in cellular signaling. As illustrated in Fig. 7**e**, structurally oriented CDs have been engineered to preserve these signaling ROS while scavenging highly toxic species like $OH^{\bullet}$ [238]. Furthermore, these CDs can generate ROS on demand under specific conditions, offering a tailored strategy to preserve tissue function by maintaining cellular redox homeostasis rather than indiscriminately eliminating ROS.

In summary, CBN-based ROS therapeutics, utilizing either ROS generation or scavenging, present a transformative approach for addressing ROS-associated disorders. The mechanisms of action, whether by mimicking enzymatic activity or through non-enzymatic pathways, underline the versatility of CBNs in restoring redox balance. However, for the successful implementation of these therapies in precision medicine, a critical gap must be addressed, which is the need for real-time detection of ROS levels in the microenvironment. Accurate monitoring is essential for understanding the dynamics of ROS fluctuations and diagnosing diseases linked to abnormal ROS levels, whether excessively high or undesirably low. Without this diagnostic capability, the therapeutic application of ROS generation or scavenging lacks the precision needed to optimize outcomes. To bridge this gap, CBN-based ROS sensing systems offer an innovative solution.

7. CBN-based ROS sensing: principles and designs

Increased ROS production is often associated with conditions such as cancer, cardiovascular diseases (e.g., atherosclerosis and myocardial infarction), neurodegenerative disorders (e.g., Alzheimer's and Parkinson's diseases), diabetes, and chronic inflammatory diseases. Conversely, decreased ROS levels can impair immune response and cellular signaling, leading to compromised wound healing or inability to fight infections. Monitoring ROS levels is essential in these contexts, as it provides insight into disease progression, therapeutic efficacy, and the overall oxidative status of the biological system. Thus, scientists have used various materials including CBNs like CDs [244], PDs [245], CNTs [246], and graphene [247,248], to detect ROS levels. This section explores how CBNs are employed in sensing through mechanisms such as Förster Resonance Energy Transfer (FRET), electrochemical detection, and fluorescence modulation (Table 3). By discussing these approaches, we aim to highlight their capabilities in addressing critical challenges in bioanalytics, and medical diagnostics, while examining their advantages and limitations in practical applications.

7.1. Förster Resonance Energy Transfer (FRET)-based sensing

FRET occurs when an energy donor fluorophore (e.g., CDs) transfers energy non-radiatively to an acceptor molecule (e.g., quencher or fluorophore) within a proximity of 1–10 nm [260]. CBNs (e.g., CDs) act as either donors or acceptors, depending on their interaction with the target analyte. Analyte-induced changes in the distance or orientation between the donor and acceptor modulate the FRET signal. The major advantage is that FRET offers high sensitivity because it depends on the distance between the energy donor and acceptor, making it useful for detecting biomolecules, metal ions, and ROS. It can also detect multiple targets when combined with different acceptors.

For example, multicolor emissive CQDs were synthesized and integrated into a FRET-based sensing platform with gold nanorods (AuNRs) for the detection of H_2O_2, glucose, glutathione (GSH), and acetylcholinesterase (AChE). The fluorescence of CQDs was turned off by AuNRs through FRET. When target analytes were present, FRET stopped, and the fluorescence turned back on, enabling measurement. The sensor was successfully applied to detect H_2O_2 in human plasma with high selectivity and excellent sensitivity (lower limit of detection ~ 75 μM) [249]. Similarly, A ratiometric fluorescence sensing platform utilizing CDs as luminophores and nanozymes was developed for sensitive H_2O_2 detection. CDs were synthesized via a simple, green, and cost-effective hydrothermal method using L-histidine as a precursor. These CDs exhibited bright blue fluorescence and peroxidase-like activity. They catalyzed H_2O_2 to produce $O_2^{\bullet-}$, which oxidized o-phenylenediamine (OPD) to form 2, 3-diaminophenolazine (DAP), enabling FRET between CDs and DAP. This interaction decreased the fluorescence of CDs and enhanced that of DAP, forming a ratiometric fluorescence analysis system. The sensor demonstrated high sensitivity and selectivity for H_2O_2 detection, showcasing the potential of CDs as dual-function luminophores and nanozymes in advanced sensing applications [250]. In another report, a turn-on fluorescence nanoprobe was developed using core–shell Ag@Au nanoparticles (Ag@AuNPs) and red emissive GQDs [251]. The probe utilized FRET for fluorescence quenching, which was reversed upon DNA cleavage by $OH^{\bullet}$ produced from a Fenton-like reaction between Ag and H_2O_2. The system exhibited a low detection limit of 0.49 μM H_2O_2 and a wide linear range (5–200 μM). It also demonstrated anti-interference and low cytotoxicity, enabling the monitoring and imaging of H_2O_2 in living cells.

Moreover, the FRET-based sensing CBNs platform was integrated with therapeutic agents for advanced theranostics of diabetic wounds (Fig. 8**a-i**) [252]. In this work, insulin and EGFs were selected to promote wound healing. For the diagnostic purposes, FRET was established by decorating porous silicon (PSi) with GQDs, resulting in the dominance of red fluorescence and the complete disappearance of blue fluorescence under normal conditions. However, in the presence of ROS, PSi underwent oxidation, leading to disruption of the FRET and the restoration of blue fluorescence. As shown in Fig. 8**a-ii,** under the induction of H_2O_2, the fluorescence gradually shifted from red to blue over time, with the most significant change observed after 10 h, which effectively distinguished varying H_2O_2 concentrations. This GQD-based platform demonstrated significant efficacy in a rat diabetic wound healing model, highlighting the potential of CBN platform for ROS regulation *in vivo*.

Table 3
Summary of CBN-based ROS sensing strategies.

Sensing mechanisms	Nanomaterial types	Applications	Representative references
FRET	CDs	Normal ROS sensing, diabetic wound healing theranostics	[249,250,251,252]
Electrochemistry	CNTs, CDs, graphene/GO	Normal ROS sensing, cancer detection, cell deformation detection	[253,254,255,256]
Fluorescence quenching	CDs, CNTs	Normal ROS sensing, cancer detection, bioimaging, wound management	[244,257,258,259]

7.2. Electrochemical sensing

Besides FRET-based sensing, CBNs, such as graphene and CNTs, can improve the electrode surface area and conductivity, enabling enhanced sensing performance [1]. Their high surface area provides more active sites for interaction with ROS. The principle of ROS sensing relies on

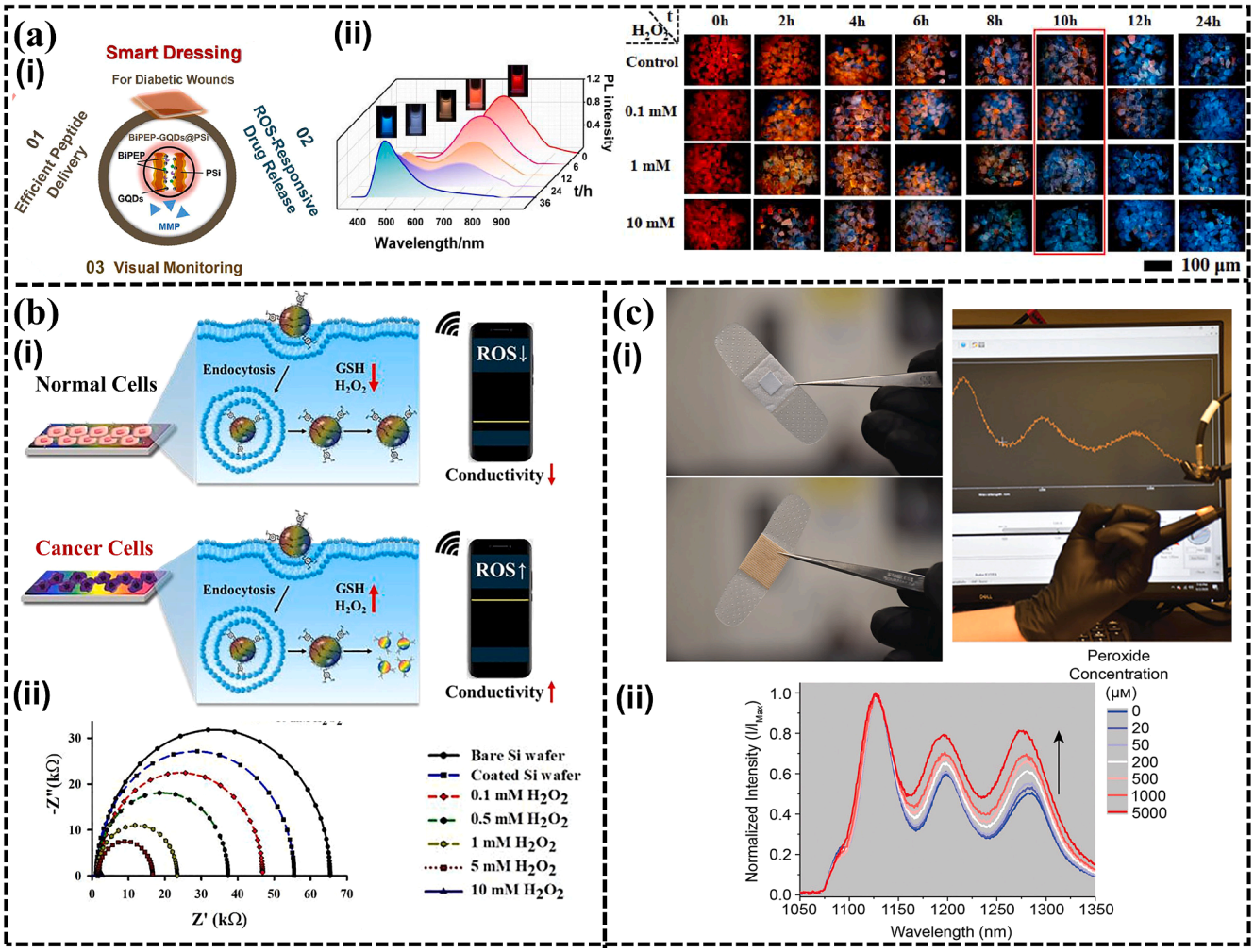

Fig. 8. CBN-based reactive oxygen species (ROS) sensing platforms: (a) Smart Förster Resonance Energy Transfer (FRET)-based ROS sensing dressing: (i) schematic illustration for leveraging both visual monitoring of ROS and therapeutic drug effects for advanced treatment of diabetic wounds; (ii) diminution of FRET effect upon induction of H_2O_2 at different time points (fluorescence gradually changed from red to blue). At the 10-hour time point, a significant difference was observed across groups with varying H_2O_2 concentrations. Reproduced with permission from [252] Copyright 2021, Elsevier; **(b)** Electrochemical-based ROS sensing platform: (i) detection of cancer by identifying ROS levels using diselenide-functionalized dopamine-conjugated hyaluronic acid polymer dots [PD(HA/DP)-DiSe] coated surface; (ii) electrochemical impedance spectroscopy (EIS) detection of H_2O_2. Higher H_2O_2 concentration resulted in lower impedance and higher conductivity. Reproduced with permission from [261] Copyright 2021, Elsevier; **(c)** Fluorescence-based ROS sensing bandage: (i) integration of single-walled carbon nanotube (SWCNT)-based optical fibrous samples into a commercial wound bandage for real time sensing of ROS; (ii) fluorescence spectra of microfibers treated with different concentration of peroxides. Higher ROS concentrations corresponded to higher fluorescence intensity. Reproduced with permission from [257] Copyright 2021, John Wiley & Sons.

redox reactions, where ROS undergo oxidation or reduction at the electrode surface [24]. For example, H_2O_2 undergoes oxidation to produce protons and O_2, while $O_2^{\bullet-}$ are reduced to generate detectable signals. These redox reactions are facilitated by the high electron transfer rates of CBNs and lead to measurable changes in electrochemical signals, such as variations in current, potential, or resistance. Common electrochemical techniques, including electrochemical impedance spectroscopy (EIS), cyclic voltammetry (CV), differential pulse voltammetry (DPV), and amperometry, are frequently used to detect these changes [262]. These methods are very sensitive, rapid, and capable of providing valuable information by detecting the ROS generated for various disease conditions.

For instance, Kim *et al.* developed a wireless ROS-sensitive sensor based on diselenide-functionalized dopamine-conjugated hyaluronic acid PDs-coated surfaces for tumor diagnosis (Fig. 8**b-i**) [261]. The sensor detected ROS through diselenide bond cleavage, resulting in structural changes that enhanced both fluorescence emission and electrical conductivity. It exhibited a resistance drop from 55.5 kΩ to 1.99 kΩ with increasing cancer cell density (10^1 to 10^6 cells mL^{-1}) and demonstrated specificity against normal cells, underscoring its potential for real-time and selective cancer detection. Meanwhile, as the H_2O_2 concentration increased from 0 mM to 10 mM, the resistance decreased from 55.5 kΩ to 1.99 kΩ (Fig. 8**b-ii**). The same group also developed a biosensor using a ureidopyrimidinone-conjugated gelatin/diselenide-bridged carbon dot hydrogel. The engineered sensor efficiently detected cancer by cleaving diselenide bonds in response to GSH or ROS. This process altered electrochemical signals and enhanced the hydrogel's self-healing and adhesiveness under tumor conditions [253].

Along with functionalized CQDs. scientists have used CNTs for detection of ROS. For example, a SWCNT/EGCG composite was fabricated by dispersing SWCNTs in green tea's antioxidant epigallocatechin gallate (EGCG). The composite detected ROS through conductance changes in response to H_2O_2, attributed to EGCG oxidation, demonstrating its potential for resistivity-based ROS sensors [254]. Interestingly, an electrochemical sensor was developed to detect mitochondrial ROS overproduction in sputum samples (<500 μL) as an early indicator

of lung cell dysfunction caused by COVID-19. The intensity of ROS emission into the sputum was measured using CV to capture the produced electrochemical signaling changes due to the binding of the ROS. The sensor demonstrated 97% accuracy and sensitivity when calibrated against clinical diagnostics from over 140 cases. Testing in four hospitals showed promise for real-time ROS-based COVID-19 detection [263]. Similarly, A stretchable and transparent electrochemical biosensor was developed using a sandwich-like structure of Au nanostructures (nano-Au) and CNT films embedded in PDMS (nano-Au/CNTs/PDMS). This platform exhibits excellent mechanical stability, biocompatibility, and electrochemical performance, detecting H_2O_2 with a wide linear range (20 nM–25.8 μM) and a low detection limit (8 nM). Real-time monitoring of H_2O_2 release from HeLa and human umbilical vein endothelial cells was achieved under stretched conditions, enabling biochemical sensing during cell deformation. This approach offers a robust solution for designing stretchable biosensors for mechanically sensitive cells [255].

There were also examples of graphene and its derivatives for the sensing of ROS. For example, Zhao *et al.* developed Fe-hemin-metal organic frameworks (MOFs) supported on a chitosan-reduced GO glassy carbon electrode (Fe-hemin-MOFs/CS-rGO@GCE) for the detection of H_2O_2 in live cells [256]. The Fe-MOF complex was employed as a support to firmly activate hemin, while CS-rGO was used to amplify the electrochemical signal. Due to the advantages of both Fe-MOFs and CS-rGO, the hemin-based electrochemical sensor was able to detect H_2O_2 released from a human serum sample and MCF-7 cells (breast cancer cells) in real-time monitoring, with an estimate of 1.1 μM of H_2O_2 released from each living cell. However, one of the main concerns with Fe-MOFs as a base substrate is the potential generation of harmful free radicals, e.g., $OH^{\bullet}$, from the interaction between Fe^{2+} and released H_2O_2 (Fenton reaction), which could lead to the deformation of the Fe-MOF structure, disrupting the sensor operation. In another report, a screen-printed carbon electrode modified with a cerium oxide nanoparticle and GO (CeNP/GO) composite was developed to detect $OH^{\bullet}$ generated by the Fenton reaction. The sensor, optimized with 8 nm CeNPs at a 50:50 CeNP:GO ratio, achieved a detection limit of 0.085 mM, demonstrating its potential for monitoring oxidative stress [264]. In addition to the amperometric and impedimetric biosensors mentioned above, a highly sensitive field-effect transistor (FET) sensor was also developed using single-layer graphene and cytochrome c (Cyt c) for the detection of H_2O_2. Graphene served as the conductive substrate, while Cyt c acted as the biomolecular receptor, enabling high-efficiency charge transfer at the Cyt c/graphene interface. The FET sensor demonstrated a rapid response time (<1 s) and an exceptionally low detection limit of 100 fM. Additionally, the sensor showed high specificity, effectively discriminating H_2O_2 from interfering substances such as dopamine, ascorbic acid, glucose, and uric acid, making it a promising platform for ROS monitoring in biomedical applications [247].

7.3. Fluorescence quenching-based detection

CBNs such as CDs, have intrinsic fluorescence properties that make them ideal candidates for ROS sensing [258]. When these nanomaterials interact with ROS, changes in fluorescence intensity occur, including quenching, enhancement, or wavelength shifts, which provide measurable "turn-on" or "turn-off" signals [258,265]. This fluorescence-based mechanism enables precise and rapid detection of ROS in biological and environmental systems. The high sensitivity of CBNs, combined with their tunable fluorescence properties, allows them to detect a wide range of ROS with remarkable specificity. Furthermore, their biocompatibility and ability to integrate with bioimaging techniques make them invaluable tools for real-time monitoring and diagnostic applications in biosensing and medical research.

For instance, De *et al.* synthesized nitrogen-doped CQDs (*N*-CQDs) for sensitive ROS detection through a peroxide-induced fluorescence quenching mechanism [244]. These *N*-CQDs were synthesized via a one-pot, eco-friendly method and exhibited high biocompatibility. This approach enabled the establishment of an empirical relationship between ROS concentration and fluorescence intensity, offering a precise and sensitive platform for real-time ROS monitoring *in vitro*. Similarly, a biotin-modified Fe^{2+}-doped carbon dot (FCDb) was developed for selective H_2O_2 detection, bioimaging, and cancer therapy. FCDb exploited Fe^{2+}-induced ROS production from H_2O_2, quenching its intrinsic fluorescence for precise sensing and imaging. It selectively targeted malignant B16F10 cells over nonmalignant NIH3T3 cells due to elevated H_2O_2 and biotin receptor expression in cancer cells. Additionally, FCDb loaded with paclitaxel (FCDb-PTX) exhibited enhanced cytotoxicity in cancer cells, emphasizing its potential as a targeted theranostic agent [259]. Xu *et al.* also used fluorescence quenching detection method to detect ROS [258]. They synthesized red emitting CDs to selectively detect $OH^{\bullet}$, $O_2^{\bullet-}$, and $^1O_2$, with no interference from H_2O_2. The fluorescence quenching upon ROS interaction was confirmed by femtosecond transient absorption spectra, showing non-radiative deactivation. Density function theory (DFT) calculations revealed a structure with pyrophosphate-linked aromatic rings, protecting the amino terminals from H_2O_2 reactivity. This work provided a metal-free nanoprobe for ROS detection and imaging.

In addition to conventional CDs, PDs have also emerged as powerful tools for detecting ROS, offering enhanced functionality and versatility. For instance, BSA-modified gold nanoparticles (AuNPs) and tellurium-containing CDs (TeCDs) were combined to fabricate Au-TeCDs nanomaterials for the detection and scavenging of $O_2^{\bullet-}$. The Au-TeCDs showed fluorescence emission at 425 and 640 nm upon exposure to $O_2^{\bullet-}$, enabling dual-fluorescence detection to quantify superoxide levels in the solution. The system also demonstrated effective $O_2^{\bullet-}$ scavenging and low cytotoxicity, making it suitable for *in situ* fluorescence imaging and scavenging excess ROS in living cells. These findings highlight the potential of Au-TeCDs for monitoring and therapeutic applications in diseased cells [32]. In another example, a redox-controlled fluorescent sensor using dihydrolipoic acid functionalized CQDs (DHLA@*N*-CQDs) was developed for ROS detection. The sensor design leveraged the redox interconversion between disulfide bonds (S-S) and thiol groups (RSH), coupling *N*-CQDs with DHLA to create a system where ROS-induced S-S formation effectively quenched fluorescence. The sensor demonstrated a wide linear range for H_2O_2 detection (0.02–90 mM), comparable to electrochemical sensors, and a response range of 0.2–600 μM for $OH^{\bullet}$, with a low detection limit of 0.12 μM. It was successfully applied for H_2O_2 determination in human saliva samples and fluorescence imaging of $OH^{\bullet}$ in HeLa cells, offering a robust tool for studying redox processes in biological systems and providing a reference for exploring other redox-active substances [266]. In contrast to CDs, CNTs have also been utilized for ROS detection, due to their excellent electrical conductivity and structural versatility. For instance, a wearable optical sensor made of core–shell microfibrous textiles with SWCNTs enabled real-time monitoring of H_2O_2 in wounds. The SWCNT-based nanosensors provided stable, non-photobleachable near-infrared fluorescence for ratiometric signal readouts. This allowed long-term and spatially resolved ROS monitoring in wound bandages (Fig. 8**c-i**) [257]. As the peroxide concentration increase from 0 μM to 5000 μM, the fluorescence intensity around 1200 nm and 1275 nm gradually increased, suggesting the high sensitivity of this SWCNT-based platform in diagnosing ROS (Fig. 8**c-ii**).

In summary, advanced nanomaterial-based sensors, including CDs, PDs, CNTs, and graphene derivatives, present promising platforms for ROS detection with high sensitivity, selectivity, and multifunctionality. However, challenges persist, including the complexity involved in synthesizing both CBNs and CBN-based ROS sensors, the scalability of the sensor fabrication process, potential cytotoxicity of CBNs and other sensor components, and interference from other biomolecules that might cause false positive or false negative results. Additionally, ensuring high stability, reproducibility, and adaptability for *in vivo*

applications of CBN-based ROS sensor platforms remains a significant hurdle. Future efforts should focus on addressing these limitations by developing robust, biocompatible, and cost-effective sensors to further enhance their diagnostic and therapeutic potential. Furthermore, ROS-based therapeutics, including generation and scavenging strategies, are anticipated to integrate with advanced sensing platforms in the future, enabling precise and adaptive ROS regulation.

8. Conclusions and future perspectives

In this review, we have systematically explored the diverse applications of CBNs in redox medicine and sensing. The ability of CBNs to either generate or scavenge ROS underpins their potential in addressing various pathological conditions, including oxidative stress-mediated diseases and cancer. CBNs demonstrate remarkable versatility through distinct mechanisms for ROS regulation. Their ROS scavenging capabilities operate via both enzymatic and non-enzymatic pathways, mimicking natural antioxidant systems. Conversely, ROS generation is often achieved through external stimuli, such as light, ultrasound, or magnetic fields, enabling precise and targeted therapeutic applications. Furthermore, their adaptability through modulation techniques, such as heteroatom doping, precursor modification, and surface functionalization, expands their scope in redox medicine.

8.1. Challenges and clinical translation

Despite significant advances in the application of CBNs in redox medicine, concerns remain regarding their biocompatibility and long-term safety, which continue to limit their clinical translation. This section addresses the biosafety of various CBNs, with particular emphasis on ROS-mediated toxicological effects.

CNTs, among the earliest and most extensively studied CBNs, have seen widespread use in energy, electronics, and structural materials. However, their biomedical application has been hindered by unresolved concerns regarding biocompatibility. While toxicity assessments have produced mixed results, multiple studies have reported adverse effects, particularly associated with MWCNTs, on pulmonary and hepatic tissues [5]. One of the main concerns is their potential to form asbestos-like structures, which can induce local ROS generation and lead to tissue and organ damage [239,240]. The U.S. National Institute for Occupational Safety and Health (NIOSH) has classified CNTs as respiratory hazards and established occupational exposure limits accordingly [267]. Graphene and GO, another widely studied class of CBNs, also warrant caution in biological applications. While they exhibit antibacterial properties through direct and indirect mechanisms, they may also compromise human cell membranes and induce oxidative DNA damage [268]. For example, the large graphene plane could interact with the cholesterol inside the lipid membrane through hydrophobic interactions and lead to membrane structure damage [269]. This membrane damage might result in increased permeability, ion imbalance, and loss of cellular homeostasis, which could eventually trigger inflammatory responses, oxidative stress, or even cell death, leading to impaired tissue function and potential physiological toxicity [270]. Fullerenes, though well-known for their ROS-scavenging potential, can also induce ROS-related toxicity when aggregated in hydrophobic forms. Soluble derivatives of fullerenes have shown better biocompatibility and are more commonly applied in antioxidant therapies [271]. Compared to the former three, CDs, however, show great biocompatibility in most of the reports, with only minor concerns related to their phototoxicity under light exposure [103,272].

From stability perspective, constructed by the strong carbon–carbon bonds, CBNs are regarded as chemically stable, which confer high resistance to degradation [273]. However, this inherent stability raises concerns about their long-term persistence in the body. Notably, some CBNs tend to aggregate in biological fluids as a result of strong π–π stacking and hydrophobic interactions. Such aggregation may promote accumulation in organs like the liver and lungs, potentially disrupting local tissue homeostasis and eliciting adverse biological effects [274].

These findings underscore the need for further preclinical research and the development of scalable, biocompatible manufacturing protocols. In summary, there are three main approaches for improving the CBNs' biocompatibility performance and accelerating clinical translations. First, since the toxicity of CBNs is closely tied to their physicochemical properties, tailoring size, hydrophilicity, and surface charge through controlled fabrication and functional group modification can significantly improve biocompatibility. For example, the cytotoxicity of fullerenes can be mitigated by introducing hydrophilic groups such as -OH or -COOH, which reduce aggregation in aqueous environments. This could be attributed to the less aggregation formation in the solution environment [191,271]. The functional group also plays an important role in the general/photo-related cytotoxicity of CDs [103,275]. Second, application scenarios should be carefully considered for CBNs. The context of CBN applications strongly influences its biosafety profile. According to Sati *et al.*'s investigations, majority of safety issues in CBN applications happen when CBNs are applied in a systemic route, particularly via the bloodstream [276]. In contrast, local applications, such as applying CBN composite materials for artificial joints and bone fusion, CBN-based drug delivery systems and bio-imaging for life-threatening disease treatment, and CBN-based particulate scaffolds for non-life-threatening treatment, typically present lower risks. This may be attributed to the reduced systemic exposure of CBNs, effectively limiting their accumulation in sensitive organs such as the lungs and liver, and thus mitigating potential cytotoxic effects. Moreover, embedding CBNs within a biocompatible polymeric scaffold can further reduce adverse biological responses by providing a protective barrier and regulating the local dosage of CBNs. Lastly, lack of standardized protocols for evaluating CBN safety contributes to variability and controversy across studies, even when tested on the same animal species. Establishing standardized operating procedures for *in vitro*, *in vivo*, and emerging AI-assisted toxicity assessments, along with clear fabrication/functionalization guidelines, will be crucial for regulatory approval and translational success.

Among the various CBNs, fullerene derivatives stand out as the most advanced in terms of potential for commercialization. This may be attributed to the fact that fullerenes were among the earliest carbon-based nanomaterials explored for their ROS-scavenging potential, resulting in extensive research into their mechanisms, efficacy, and formulation strategies. As a result, stable and biocompatible forms have been developed to overcome concerns about ROS-related toxicity associated with their hydrophobic aggregation. Notably, fullerene derivatives are already marketed in Japan under the brand name "Radical Sponge" as antioxidant agents in cosmetic and skincare products [277]. However, most other CBNs, including GO, CNTs, and CDs, remain confined to research or preclinical stages due to lingering biosafety and scalability issues. Moving forward, once these barriers are addressed, several areas of clinical practice could benefit from CBN-based technologies. For instance, the therapeutic effects of established ROS-regulating drugs, such as Edaravone [278], N-Acetylcysteine (NAC) [279], and AREDS formula [280], could potentially be enhanced by co-delivery with highly soluble, ROS-scavenging CBNs like fullerenes or CDs. Additionally, CBN-based sensing platforms may offer improved sensitivity and selectivity in detecting ROS-related pathophysiology compared to current techniques such as enzyme-linked immunosorbent assays (ELISA). Furthermore, the intrinsic fluorescence properties of CDs may support intraoperative imaging applications, including real-time detection of residual tumor tissues, similar to ongoing clinical trials using fluorescent probes [281].

8.2. Development of "sensing plus" platform

The integration of ROS-based therapeutics with sensing platforms has emerged as a promising avenue for precision medicine. Real-time

monitoring of ROS levels is critical for understanding disease progression, enabling targeted interventions, and achieving optimal therapeutic outcomes. While current research demonstrates significant advances in this field, challenges remain in achieving a seamless combination of ROS regulation and sensing within complex biological systems.

A promising future direction lies in the development of advanced "sensing-plus" devices, which integrate enhanced sensing capabilities with therapeutic functions, enabling real-time monitoring and targeted intervention for various medical applications. While various studies have been focused on combining sensing with ROS therapies, such as generation and scavenging, for precise control, these applications are still mostly confined to *in vitro* studies and have yet to be translated into *in vivo* or clinical settings [32,258,259]. Emerging technologies, such as injectable biosensors or non-invasive real-time monitoring approaches, hold significant potential in advancing these applications. For instance, using injectable hydrogels or other delivery systems to administer sensors to internal tissues, combined with ultrasound or magnetic field-based real-time monitoring, could enable more precise control and monitoring of ROS levels *in vivo*, paving the way for enhanced therapeutic efficacy [282,283]. For CBN applications in deep tissue, techniques like NIR light and ultrasound could be employed to precisely regulate ROS generation and scavenging on demand. Under normal conditions, CBNs would persist in a scavenging state, offering sustained protection against ROS. Their activity, however, can be precisely activated or modulated through external stimuli, enabling targeted therapeutic intervention when required. Although previous research trials have demonstrated the potential to modulate the on/off switching of the pro-oxidant state [104,135,237] (similar to "sensing plus"), further advancements are required to refine this approach for precise therapeutic applications.

While both real-time monitoring and non-invasive tuning have been demonstrated individually, combining these strategies could offer a more effective approach for managing ROS-related diseases. By integrating these technologies, it may be possible to precisely regulate ROS levels in real-time, enhancing therapeutic outcomes and enabling more targeted treatments for complex ROS-mediated diseases. This integration could lead to significant advances in the treatment of conditions such as cancer, neurodegenerative disorders, and inflammatory diseases, where ROS play a critical role.

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Appendix A. Supplementary data

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