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Review

Carbon Nano-Onions in Biological Applications: Recent Progress and Future Directions

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Abstract
Carbon nano-onions (CNOs), together with graphene and its derivatives, are one of the most interesting carbon nanostructures due to their peculiar chemical and physical properties. Made of a number of concentric fullerene layers, carbon-based structures have a peculiar design and assume the appearance of onion-like cages. Due to their excellent biocompatibility and safety, CNOs have low toxicity, high water dispersibility (due to surface functionalization), and high pharmacological efficacy. These properties render them highly appealing for applications such as drug delivery, sensing, imaging, tissue engineering, and therapeutic agents. While CNOs were discovered almost at the same time as other carbon nanomaterials (CNMs), their potential in biological applications remains largely unexplored. On the other hand, similar to other CNMs and fullerenes, CNOs play a crucial role as they represent carbon's ability to form diverse nanostructures with exceptional properties. This review aims to summarize recent studies on CNOs for biological applications, underlining the current achievements, possible opportunities, and challenges toward future development.

1. Introduction

Carbon nanomaterials (CNMs) have drawn a lot of attention in the past 10 years because of their unique qualities, which include high conductivity, low friction coefficient, high hardness, thermal resistance, and chemical stability [1]. These nanomaterials, with sizes between 1 and 100 nm, are characterized by a high surface-to-volume ratio and are, therefore, being exploited in applications related to regenerative medicine, drug delivery, imaging, and sensing. These include graphene, CNTs, carbon dots (CDs), fullerenes, and CNOs. Carbon nano allotropes could act as a bridge between carbon materials and organic molecules, providing nanoplatforms with several combined functionalities [2–4].

Carbon nano-onions have attracted particular interest due to their remarkable biocompatibility and low toxicity, as demonstrated by cytotoxicity assessments conducted on HeLa and fibroblast cell lines using standard assays such as MTT and LDH [5–7]. First proposed by Iijima, CNOs are materials made up of onion-like homocentric graphitic layers. While CNOs share structural similarities with fullerenes, they exhibit fundamental differences in composition and electronic properties. Such a structure allows the hosting of various atoms and molecules inside the internal space and can be easily doped. Under these circumstances, the graphitic inner structure would facilitate electron transfer within the host, and the porous inner shells act as dual active layers [8, 9]. The increased surface area, by the formation of interconnected ion channels through endo- and exohedral pores, enhances the storage efficiency. Such cage-like structures with defects have excellent catalytic and electrocatalytic properties, finding applications in sensing, drug delivery, water purification, cell imaging, and supercapacitors. Besides, mesoporosity and high surface area render CNOs the ideal energy storage material [4, 10, 11].

This review covers the applications of CNOs in biological and biomedical fields, such as their application as imaging agents, drug delivery systems, tissue engineering, and sensors. Despite their huge potential, the role of CNOs in biological applications has been neglected for many years [12]. Nevertheless, CNOs have played significant roles in areas like sensing and catalysis, hence becoming a promising platform for novel biomedical approaches. More than that, rapid development within the application of nanomaterial biomaterials underlines a great application opportunity for CNOs in the food, environment, medicine, and agriculture fields, needing further study for their potential fulfillment.

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2. Synthesis Approaches and Properties of CNOs

The synthesis of CNOs involves methods such as electron beam irradiation, arc discharge, annealing, chemical vapor deposition (CVD), pyrolysis, and ion implantation, which are categorized into low-yield and high-yield production techniques [13–19]. The discovery of CNOs began when Iijima observed spherical, shell-like structures with diameters of 5–20 nm during the analysis of carbon black produced by vacuum evaporation of graphite[7, 20]. In 1992, Ugarte and colleagues produced CNOs with sizes ranging from 6–50 nm by irradiating carbon soot in a high-resolution 300 kV electron microscope [21]. Among these methods, annealing is one of the most efficient and high-yield techniques, requiring extremely high temperatures (2200–2400°C) to break carbon-carbon bonds [22]. Kuznetsov and colleagues introduced a low-temperature annealing method using nanodiamonds as the starting material, operating at milder temperatures (1000–1500°C) with nearly 100% yield [22]. This method has become highly popular for industrial applications due to its efficiency. Other high-yield methods include arc discharge and CVD, which enable the synthesis of CNOs with varying sizes and properties depending on the starting materials and conditions [23]. For instance, Xu and colleagues optimized the arc discharge method, producing homogeneous CNOs with sizes of 20–50 nm.

CVD is particularly effective for producing metal-containing CNOs using catalysts such as Fe, Co, and Ni. This method also allows for catalyst-free production, yielding pure and easily separable CNOs [24–26]. On the other hand, pyrolysis is a cost-effective method that utilizes raw materials such as biomaterials and plastic waste. Thripati et al. produced CNOs (4–8 nm) with stable green photoluminescence via flaxseed oil pyrolysis [26], while Singh et al. synthesized CNOs using lycopene extracted from tomatoes [27]. Ion implantation, another promising technique, involves implanting carbon ions onto copper or silver surfaces, with parameters like temperature and dose affecting the size and uniformity of the CNOs.

Waste pyrolysis offers an eco-friendly approach, producing CNOs sized 6–10 nm, which further emphasizes this technique's sustainable applications. Among all methods, Kuznetsov's low-temperature annealing stands out for its affordability and efficiency [17]. At the same time, both CVD and pyrolysis are valued for their cost-effectiveness and versatility in using diverse raw materials.

3. Biological Applications

3.1. Bioimaging

Fluorescent carbon nano-onion (CNO)- based nanoprobes are promising alternatives to molecular probes due to their brightness, photostability, and non-toxic nature. However, most existing CNOs lack fluorescence. To address this, green/red/NIR-emitting dyes are attached to CNOs via covalent or non-covalent interactions to impart fluorescence, or self-fluorescent CNOs are synthesized without the need for additional dyes [28, 29]. Ghosh et al. synthesized water-soluble fluorescent CNOs by pyrolyzing wood wool, which showed imaging capabilities in *Drosophila melanogaster* and the ability to cross the blood-brain barrier. Carboxylated CNOs exhibited broad-spectrum fluorescence (QY ~ 3%) and multiple emissive properties due to surface defects [30]. Dubey et al. produced fluorescent CNOs from camphor and polystyrene foam with low QY (~1.5-1.65%) and used them for E. coli imaging [31]. Similarly, Tripathi et al. synthesized multi-emissive CNOs (QY ~ 17%) from vegetable ghee for bioimaging [32]. Recently, white-light-emitting CNOs (QY ~ 10%) were developed via the pyrolysis of sodium deoxycholate and applied in bioimaging and biosensing.

Bartelmess et al. (fig. 1A) described a novel method for employing pyrene-BODIPY conjugates formed on the CNO surface by π-π stacking to functionalize carbon nano-onions (CNOs) via non-covalent interactions. The resulting fluorescent carbon nanoparticles were successfully internalized by HeLa cancer cells without exhibiting cytotoxicity [33]. Frasconi et al. (fig. 1B) demonstrated the targeted imaging of cancer cells by covalently modifying carbon nano-onions (CNOs) with folic acid and fluorescein. In two cancer cell lines, the functionalized CNOs demonstrated outstanding brightness, photostability in aqueous conditions, and effective, selective absorption without discernible harmful effects. Using a combined confocal and transmission electron microscopy approach, the CNOs were localized in late-endosome compartments within the cells [34].

Various studies have demonstrated that CNOs can be used in in vitro imaging techniques, such as cell imaging, and *in vivo* imaging applications. Revuri et al. (fig. 1C) detailed the fabrication of water-soluble, biocompatible, single-phosphor white-light-emitting carbon nano-onions (WCNOs) and their application as novel multichannel fluorescence nanoprobes for bioimaging and biosensing. While in vitro and in vivo experiments showed their absorption and multichannel fluorescence emission in blue, green, and red channels, FE-TEM verified the effective synthesis of WCNOs. Additionally, WCNOs showed enhanced tumor accumulation with safe liver and kidney elimination. Manganese oxide (WCNO-MnO_2) nanosheets were applied to WCNOs in order to investigate their stimuli-responsive potential; these nanosheets muted

their fluorescence but interacted with glutathione (GSH) in biological settings. The findings demonstrated that GSH restored the fluorescence of WCNOs by etching the MnO_2 layer. In vitro and in vivo studies further confirmed GSH-responsive multichannel bioimaging, establishing WCNOs as a promising, biocompatible tool for diverse biomedical applications [36].

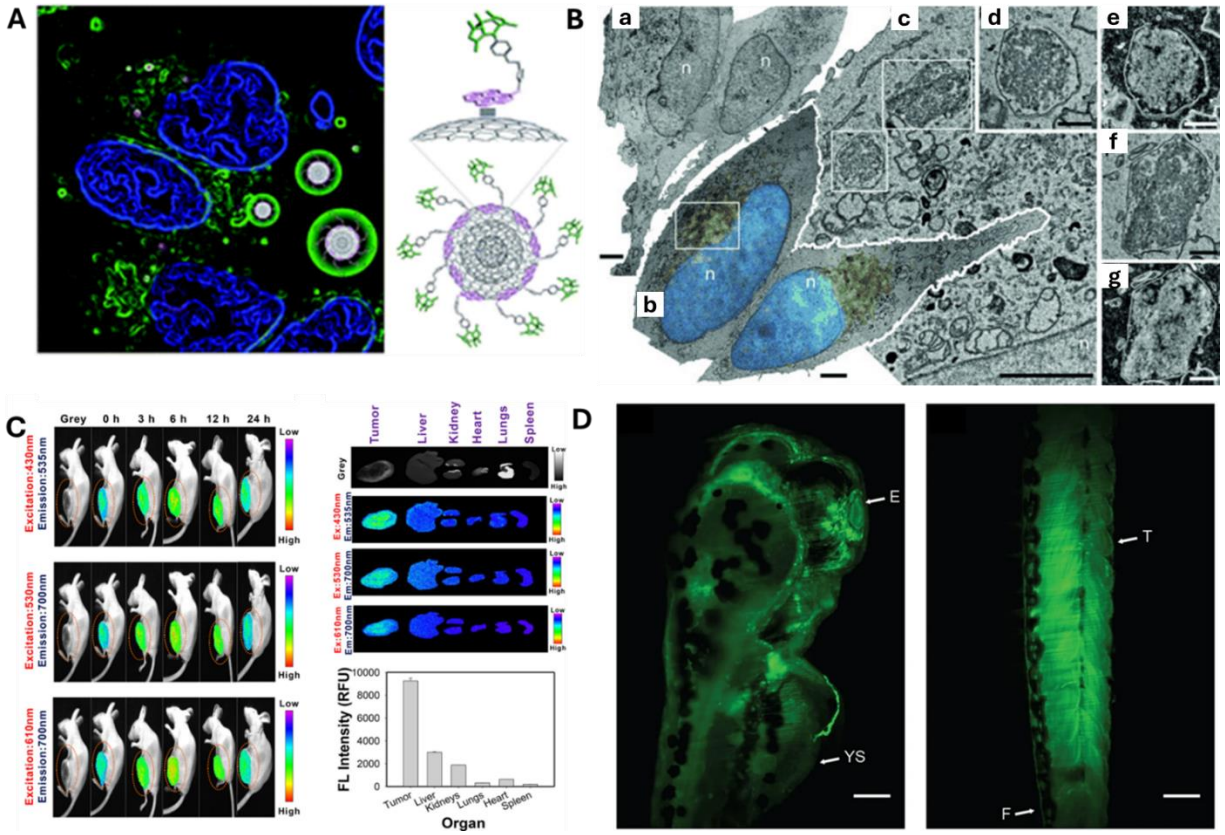

Figure 1. A. Pyrene-BODIPY conjugates assembled on CNOs via π-π stacking are successfully uptaken by HeLa cells without observed cytotoxicity and reprinted with permission from [35] **B.** Correlative light and electron microscopy analysis of HeLa cells treated with FA/FITC–CNO (10 μg/mL, 12 h, 37 °C) reveals colocalization of FA/FITC–CNO (green) within lysosomes, resulting in yellow fluorescence. TEM and HAADF imaging confirm the presence of FA/FITC–CNO in endosomes.Reprinted with permission from [35] **C.** In vivo and ex vivo multichannel fluorescence imaging shows time-dependent accumulation of WCNOs in tumor regions (0–24 h) and their distribution in various organs after 24 h, with quantitative analysis confirming tissue-specific accumulation. Reprinted with permission from [36] **D.** Maximum intensity projections of the superior part and tail of larvae treated with BODIPY-CNOs (100 μg/mL) reveal detailed structures, including the eye, yolk sac, tail, and finfold—scale bars: 100 μm. Reprinted with permission from [37].

Amora et al. (fig. 1D) investigated the biological impact of functionalized carbon nano-onions (f-CNOs) on zebrafish development, assessing toxicity endpoints such as survival rate, hatching rate, and heart rate. A biodistribution study of boron dipyrromethene (BODIPY)-functionalized CNOs was conducted using inverted selective plane illumination microscopy (iSPIM), enabling rapid 3D imaging. The in vivo results demonstrated that f-CNOs exhibit no toxicity, high biocompatibility within the concentration range of 5–100 μg mL^{-1}, and a homogeneous biodistribution in zebrafish larvae, highlighting their potential for imaging, diagnostic, and therapeutic applications [37].

3.2. Drug delivery and therapeutic applications

Drug delivery methods are essential for improving site-specific localization, which reduces off-target toxicity and increases drug therapeutic efficacy. Along with overcoming obstacles to systemic circulation, these systems are essential for moving therapeutic compounds from the point of administration to the target location. The capacity to transport a sufficient quantity of therapeutic molecules and shield the payload until it reaches the intended destination are essential characteristics of the perfect drug delivery vehicle. Furthermore, biosafety and biocompatibility are crucial aspects that need to be taken into account for efficient medication distribution [38–40].

Among carbon-based nanomaterials (CNMs), carbon nano-onions (CNOs) stand out as promising candidates for drug delivery systems (DDS). CNOs can remain in systemic circulation for extended periods, increasing their likelihood of reaching the target site. Studies have shown that these carbon-based nanostructures exhibit minimal toxicity and low inflammatory potential, making them highly biocompatible. Furthermore, they are ideal for drug delivery applications because of their huge surface area and accessible pi-electrons. Therefore, this section explores the potential of CNOs as a drug-delivery system [38, 39].

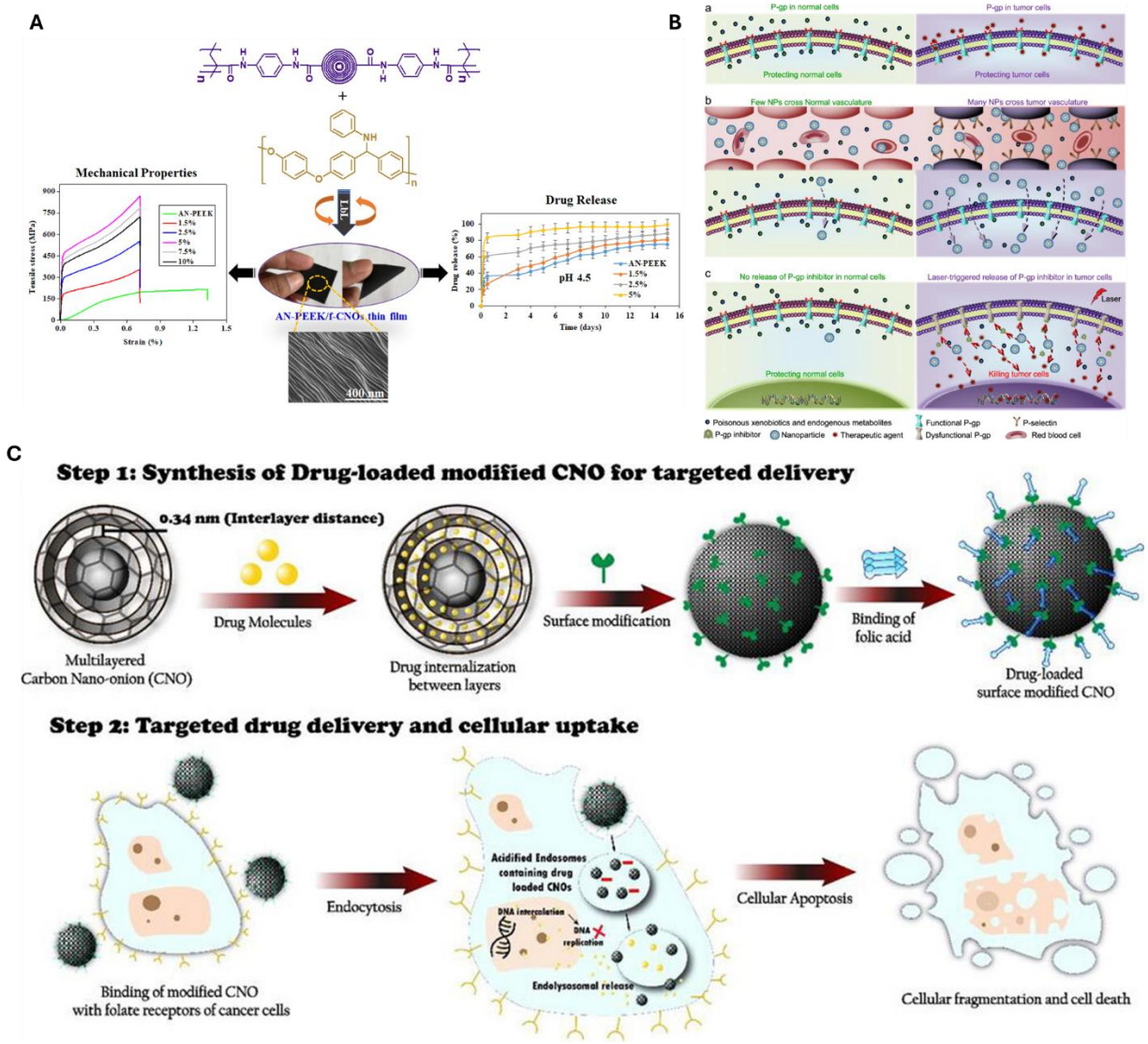

Figure 2 A. AN-PEEK/f-CNOs composite thin films synthesized via LbL self-assembly exhibit improved mechanical properties and pH-responsive drug release behavior. Reprinted with permission from [41]. **B.** Mechanism of tumor-targeted nanoparticles (NPs) for overcoming P-gp-mediated drug resistance. (a) P-gp pumps in normal cells protect against xenobiotics, while in tumor cells, they exclude therapeutic agents. (b) NPs selectively accumulate in tumor vasculature via active P-selectin targeting and the EPR effect, with minimal entry into normal cells. (c) Laser-triggered release of therapeutic agents and P-gp inhibitors in tumor cells disables P-gp pumps, enabling drug efficacy while sparing normal cells due to limited NP accumulation and release. Reprinted with permission from [42]. **C.** The schematic of functionalized carbon nano-onions (f-CNOs) for targeted drug delivery. (Step 1) CNOs are loaded with BCNU, surface-modified, and functionalized with folic acid. (Step 2) f-CNOs bind to cancer cell receptors, enabling drug delivery, mitochondrial dysfunction, ROS production, and apoptosis, leading to cancer cell death. Reprinted with permission from [43].

Mamidi et al. synthesized (fig. 2A) anilinated-poly(ether ketone) (AN-PEEK) and poly(N-(4-aminophenyl) methacrylamide)-carbon nano-onions (PAPMA-CNOs, also known as f-CNOs) were used to create AN-PEEK/f-CNOs composite thin films for stimuli-responsive drug release through layer-by-layer (LbL) self-assembly. Over the course of 15 days, the release of doxorubicin (DOX) from these thin films showed regulated pH-responsive drug release, reaching 99.2% at pH 4.5 and 59.3% at pH 6.5. The supramolecular π significantly influenced the regulation of drug release–π

stacking interactions between f-CNOs and DOX. Cell viability studies with human osteoblast cells showed enhanced cell viability, while the films exhibited impressive mechanical properties, including tensile strength (891.4 ± 8.2 MPa), Young's modulus (43.2 ± 1.1 GPa), and toughness (164.5 ± 1.7 Jg^{-1}). Quantitative analysis suggested that the well-aligned nanofibers created a critical interphase, contributing to the superior tensile properties. These pH-responsive and mechanically robust biocompatible thin-film systems hold promise for biomedical applications [41].

Wang et al. developed (fig. 2B) fucoidan-decorated silica-carbon nano-onion (FSCNO) hybrid nanoparticles designed to target tumor vasculature for the selective release of a P-glycoprotein (P-gp) inhibitor and an anticancer drug into tumor cells. The tumor-targeting capability of these nanoparticles was validated across multiple models. Additionally, the nano-onions demonstrated excellent light absorption in the near-infrared (NIR) region, enabling triggered drug release under low-power NIR irradiation. The released P-gp inhibitor selectively bound to P-gp pumps, effectively disabling their drug efflux function and enhancing the intracellular bioavailability of the anticancer drug. Notably, while free P-gp inhibitors significantly increased the systemic toxicity of chemotherapy drugs, this issue was mitigated through FSCNO nanoparticle delivery combined with short, low-power NIR laser irradiation [42]. Majumder et al. introduced (fig 2C) a novel approach to drug delivery using carbon nano-onions (CNOs) functionalized with bis-chloroethyl nitrosourea (BCNU/carmustine) to achieve targeted and sustained drug release. The autofluorescent nature of the functionalized CNOs (f-CNO–BCNU) allowed for in vivo tracking, while TEM and DLS analyses characterized their size. Binding studies revealed that f-CNO–BCNU interacts noncovalently with folate receptors (FRα) on cancer cells, supported by polar stabilization from Asp55 and Glu86 residues, with a binding free energy of −29.9 kcal/mol. The system demonstrated effective cancer cell targeting, reducing cell viability at low IC50 values, and inducing mitochondrial dysfunction, ROS production, and apoptosis, as confirmed by Franz diffusion and Annexin V assays. This biocompatible and efficient system shows promise as a smart chemotherapeutic agent, enhancing carmustine bioavailability and offering improved therapeutic outcomes [43].

3.3. Sensor applications

In recent years, several studies have explored the use of CNO-modified surfaces for examining biomolecular interactions. This has been made possible by the large surface area of CNOs and their enhanced electron transfer capabilities. However, research in this area remains limited. Therefore, this section of the article focuses on the applications of CNO-modified electrodes and fluorescence sensors [44, 45].

Bartolomé et al. modified diazonium salts with carboxylic acid and maleimide groups electro grafted onto glassy carbon electrodes to create tiny carbon nano-onions (CNOs). Using ESEM, AFM, and electrochemical methods, the CNO-modified surfaces were utilized to identify a model DNA sequence linked to human HPV. Amidation or thiol-maleimide reactions were used to immobilize short recognition sequences. Compared to unmodified electrodes, CNO incorporation improved sensitivity. It lowered detection limits due to the increased surface area and enhanced electron transfer properties, demonstrating the potential of CNO-based platforms for biomolecule detection [46].

Sok et al. developed (fig. 3A) a biosensor that uses carbon nano-onions (CNOs) as electrode materials because of their high conductivity and biocompatibility to detect the phenoxy-based herbicides 2,4-D and 2,4,5-T. Peroxidase on CNOs was immobilized within a cyclodextrin polymer matrix to create the biosensor. The mechanism by which 2,4-D and 2,4,5-T impair peroxidase activity was examined using molecular docking studies and activity testing. Electrochemical and microscopy methods were used to characterize the biosensor, and its use showed improved sensitivity, stability, and reproducibility. The biosensor was effectively used to identify 2,4-D in soil and 2,4,5-T in samples of river water [47]. Zou et al. addressed (fig. 3B) the difficulties in developing pressure sensors with both high sensitivity and a broad pressure response range, especially for applications including sleep health monitoring. Using a synergistic enhancement technique based on material properties and microstructure design, they combined a triboelectric pressure sensor (TPS) and a piezoelectric pressure sensor (PPS) to create a hybrid pressure sensor (HPS). A straightforward, affordable, and structurally adjustable technique was used to combine carbon nano-onions (CNOs) with Ecoflex for the TPS in order to investigate the effects of CNOs and hierarchical microstructures on electrical performance. In order to lower the detection limit and increase the pressure response range, the PPS component was added. The resultant HPS showed a low detection limit of 10 kPa, a wide response range of up to 1200 kPa, and a high sensitivity of 2.46 $V/10^4$ Pa (within the 50–600 kPa range). It also demonstrated a quick response time and outstanding stability over 100,000 cycles. The HPS-based sleep monitoring system shown its potential for use in disease prediction and sleep health monitoring by successfully identifying breathing patterns and monitoring sleeping postures [48].

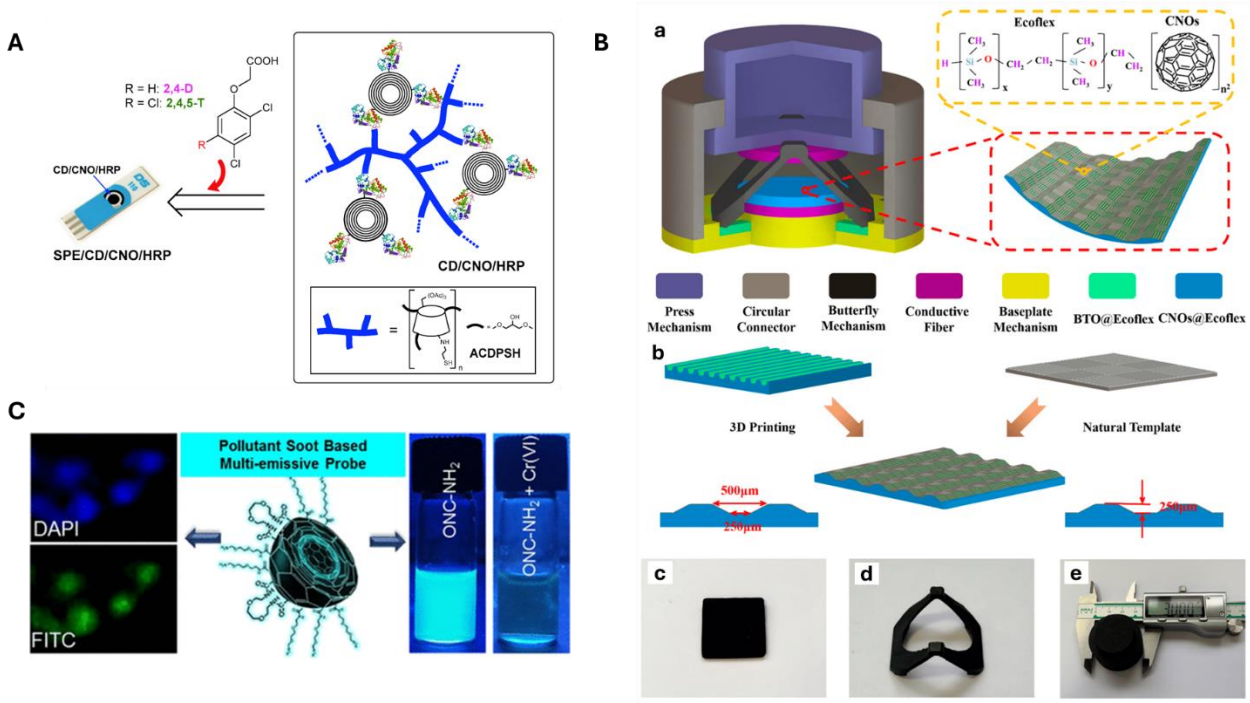

Figure 3 A. Preparation of SPE/CD/CNO/HRP electrodes for electrochemical detection of 2,4-D and 2,4,5-T. Reprinted with permission from [47] **B.** Shows the design of a carbon nano-onion-based hybrid pressure sensor (HPS). (a) HPS schematic. (b) Preparing a hierarchical composite microstructure. (c) A picture of the Ecoflex CNOs. (d) A picture of the mechanism of the butterfly. (e) HPS photograph. Reprinted with permission from [48]. **C.** This study utilizes black carbon (BC) from diesel soot to produce water-soluble, amine-functionalized onion-like nanocarbons (ONC-NH_2) as fluorescent probes for cancer cell imaging (HeLa) and Cr(VI) detection in water, with surface functionalization analyzed via spectroscopy. Reprinted with permission from [49].

As a fluorescent sensor, this study (fig. 3C) describes a sustainable approach utilizing black carbon (BC) derived from diesel soot to isolate onion-like nanocarbons (ONC), which are then surface-functionalized to create water-soluble amine-functionalized ONC-NH_2 with a high quantum yield of ~20%. Instead of synthesizing ONCs explicitly, they were isolated directly from diesel soot and converted into efficient, biocompatible fluorescent probes through amine functionalization. These ONC-NH_2 probes demonstrated excellent performance in imaging HeLa cancer cells and selectively detecting toxic chromium Cr(VI) in water. The detailed amine surface functionalization, enabling aqueous solubility, was characterized using spectroscopic techniques such as XPS, NMR, and FTIR. This sustainable approach highlights the potential for transforming waste materials into valuable tools for biomedical and environmental applications [49, 50].

4. Conclusion and Future Perspective

We have reviewed the synthesis methods of CNOs and their potential in biological applications. Features such as low toxicity, high biocompatibility, efficient cellular uptake, and suitability for surface modification make CNOs strong candidates as imaging probes and therapeutic agent carriers. In particular, eco-friendly surface functionalization methods enhance the water dispersibility of CNOs, enabling a broader range of applications in biological fields. Additionally, the combination of these surface functionalization strategies with covalent and non-covalent modifications positions CNOs as promising nanomaterials for biosensor applications. Recent studies demonstrate that CNOs stand out as exceptional candidates among nanomaterials designed for diagnostic and therapeutic purposes, thanks to their remarkable properties. In the future, innovations in the engineering and design of these carbon materials could expand their applications in complex areas such as the diagnosis and treatment of neurodegenerative diseases. However, the limited number of studies on the in-vivo use of CNOs remains a drawback. Therefore, more research is needed to highlight their potential in this field.

Acknowlegments
This review includes a part of the doctoral thesis.

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