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Review

Green Approaches to Carbon Nanostructure-Based Biomaterials

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Abstract: The family of carbon nanostructures comprises several members, such as fullerenes, nano-onions, nanodots, nanodiamonds, nanohorns, nanotubes, and graphene-based materials. Their unique electronic properties have attracted great interest for their highly innovative potential in nanomedicine. However, their hydrophobic nature often requires organic solvents for their dispersibility and processing. In this review, we describe the green approaches that have been developed to produce and functionalize carbon nanomaterials for biomedical applications, with a special focus on the very latest reports.

Keywords: carbon nanostructures; graphene; carbon nanotubes; carbon nanodots; nanodiamonds; nanomaterials; biomaterials

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1. Introduction

The family of carbon nanostructures (Figure 1) comprises of many different members that generally share the common feature of being composed of carbon atoms, covalently bound in a sp^2 hexagonal lattice, although exceptions exist [1]. The two-dimensional (2D)-sheet of graphene can be considered as a universal building block, which, depending on how it is folded, can give rise to 0D fullerenes [2], 1D single-wall [3] or multi-wall [4] carbon nanotubes (CNTs), or 2D-graphene-based materials [5]. Other nanostructures comprise nano-onions (CNOs) [6], nanohorns (CNHs) [7], nanocones, and nanodiscs [8]. Nanodiamonds (NDs) differ for they contain a large portion of sp^3 carbon atoms [9]. More recently, carbon dots have acquired increasing attention [10]. Furthermore, carbon nanostructures can be assembled together in superstructures [11] and 3D-materials [12].

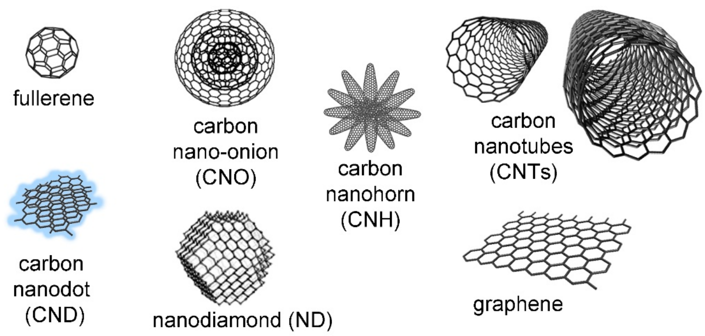

Figure 1. Carbon nanostructures discussed in this review (not to scale). The nano-onion schematic structure is reproduced with permission from [13], copyright ©1995, Elsevier.

Each of these components has its own unique properties related to the specific morphology, size, and reactivity. They generally feature very interesting electronic conductivity, high mechanical strength, low density, as well as the ability to undergo chemical functionalization to further tune their properties as needed for the intended application. It is thus not surprising that many reviews already exist on their clinical applications [14] in biomedicine [15–17] and, above all, on their potential use in oncology [18], such as innovative components in cancer theranostics [19] and cancer therapy [20], thanks to their ability to target the tumor micro-environment [21]. Indeed, the possibility to use them not only as vehicles for drug delivery [22], but also for innovative imaging [23] and biosensing [24], makes them ideal candidates for innovative theranostics [25,26].

Research is also very active on their applications to target diseases other than cancer, such as atherosclerosis [27], and infections [28], including the recent fight against coronaviruses [29]. Further areas of intense investigation include tissue engineering [30], in particular to reconstruct the heart [31] and to re-establish neural connections [32], due to their demonstrated ability to boost the electrical activity of conductive tissue [33] and stimulate nerve growth [34]. Finally, there has been increased interest in their electron-conductive abilities, to develop innovative wearable electronics [35].

Interactions between carbon nanomaterials and biomolecules, especially DNA [36] and proteins [37], are the object of many investigations, due to their role in determining the dynamic structure of the biomolecular corona [38], which ultimately affects the response in vivo [39], e.g., the biodistribution [40], the immune response [41], for instance mediated by neutrophils [42], and, thus, the biodegradation [43].

Despite decades of research efforts in these sectors, there are still many concerns regarding carbon nanostructure toxicity [44,45] and immunogenicity [46], also due to the high heterogeneity of this class of materials, which present both unexploited opportunities and unresolved challenges [47] in nanomedicine. In particular, one of the latter regards the large-scale production for mainstream applications [48], considering the current emergency we are facing, in terms of preservation of the environment, especially the development and implementation of green routes for their sustainable production.

Therefore, in light of the vastness and complexity of the topic of carbon nanomaterials for biomedical applications, this concise review aims to cover only the most recent advances in the nanomedicine area that describe green chemical routes for their preparation and chemical modifications, in the hope that it will inspire scientists that enter this area towards more environmentally conscious choices for their chemical procedures.

2. Green Routes to Prepare Carbon Nanomaterials for Biomedical Applications

In recent years, researchers have been paying more attention to green routes for the production of carbon-based nanomaterials, as well as for biomedical applications, and the topic was reviewed recently for specific types of nanostructures, especially carbon quantum dots (CQDs) [49,50]. However, this is a very active field of prolific research and many new reports continue to appear at a fast pace in the literature. Therefore, in this work, we will focus on the most recent examples that will be organized based on the type of nanostructure produced, in particular fullerenes, nano-onions, CQDs, nanodiamonds, nanohorns, CNTs, and 2D-graphene-based nanomaterials. Table 1 details the type of nanostructure, green route employed, carbon source, and solvent used, and the envisaged application for the most recent reports that discuss the preparation of various types of carbon nanomaterials in their pristine form, as well as their reduction and oxidation, which are often the first step to fine-tune their properties for biological uses.

Table 1. Recent examples of green methods to produce carbon nanostructures, their oxidized and reduced forms, suitable for biomedical applications.

Carbon Nanostructure	Green Route	Carbon Source	Solvent	Application	Reference
Fullerenes [1]	Catalytic thermal decomposition	Plastic waste	n.a.	n.a.	[51]
Nano-onions	Carbonization	Tomatoes	Water	Theranostics	[52]
	Hydrothermal	Citric acid	Water	n.a.	[53]
CQDs	Calcination	Gynostemma plant	Water	Bioimaging Antioxidant	[54]
	Electrochemistry	Graphite	Water/ethanol	Radioimaging	[55]
	Gamma irradiation	Graphite	Water/ethanol	Photodynamic therapy	[56]
	Hydrothermal	Chitosan	Water	pH sensing	[57]
	Hydrothermal	Cyanobacteria	Water	Composites	[58]
	Hydrothermal	Fruit flesh	Water	Ag^+ sensing Bioimaging	[59]
	Hydrothermal	Fruit juice	Water	Bioimaging Hg^{++} sensing	[60]
	Hydrothermal	Fruit peel	Water	Fe^{+++} sensing	[61]
	Hydrothermal	Fruit waste	Water/ethanol	Bioimaging Fe^{+++} sensing	[62]
	Hydrothermal	Green tea	Water	Photodynamic therapy	[63]
	Hydrothermal	Red cabbage	Water	Fluorescent ink Antioxidant	[64]
	Hydrothermal	Sugarcane bagasse pulp	Water	Antibacterial	[65]
	Hydrothermal	Wheat straw	Water	Bioimaging F^- sensing	[66]
	Microwave	Cellulose	Water	Biomaterials	[67]
	Microwave	Roasted chickpeas	Water	Bioimaging Fe^{+++} sensing	[68]
	Pyrolysis	Citric acid	Water	Hg^{++} sensing	[69]
	Pyrolysis	Zingiberis rhizoma	Water	Analgesic	[70]
	Sand bath	Fruit peel	Water	Bioimaging	[71]
	Sonochemical	Gelatin	Water	Bioimaging	[72]
NDs	Laser ablation	Coal	Ethanol	n.a.	[73]
oxidized NDs [2]	Microplasma jet	NDs	Water	n.a.	[74]
oxidized CNHs [2]	UV/H_2O_2 oxidation	CNHs	Water	Drug delivery	[75]
oxidized CNTs [2]	UV-ozone	CNT fibers	n.a.	Electronics	
GO [2,3]	Electrochemical	Graphite	Acidic water	(Bio)materials	[76]
	Photoelectrochemical	Graphite	Water	(Bio)materials	[77]
rGO [2,3]	Mushroom-extracted reductant	GO [3]	Water	n.a.	[78]
	Cysteine reductant	GO [3]	Water/ethanol	Drug delivery	[79]
	Ascorbic acid reductant	GO [3]	Water	Neuroscience	[80]

[1] magnetic derivative composite. [2] the green route refers solely to the functionalization of the nanocarbon and not the preparation of the carbon nanostructure scaffold used as starting material. [3] (r)GO = (reduced) graphene oxide.

2.1. Fullerenes

Fullerenes are spheroidal molecules composed solely of carbon, of which the most widely known is C_{60}, composed of 60 carbon atoms. Their nanosize and peculiar electronic properties rendered them the subject of many investigations for potential uses in nanomedicine [81], including drug delivery [82], photodynamic [83], antioxidant [84,85], and even antiviral [86] therapy.

Fullerenes can be synthesized by many methods, which mainly involve the vaporization of graphite or similar carbon sources, and that include arc-evaporation, pyrolysis, radio-frequency plasma, or laser ablation. Moreover, fullerenes purification requires large volumes of organic solvents due to their generally low solubility [81]. Therefore, the development of green procedures for their preparation is not at all trivial. However, the use of microwaves [87] can be beneficial in reducing reaction times and temperatures, although even this convenient development has not solved the many challenges faced by the industry to produce fullerenes at a low cost [88].

It is worth noting that fullerenes need to be derivatized to be water-soluble in appreciable concentrations for biomedical applications; therefore, opportunities for the green synthesis of fullerenes may lie in the preparation of those derivatives. For instance, hydrophilic polydopamine and glutathione were used to solubilize fullerenes by simple mixing in water, followed by dialysis and freeze-drying, to then study their antioxidant activity [89]. Sonochemical treatment in water of a mixture of fullerene and gallium oxide yielded nanostructured hybrids with potential applications in the field of sensing [90]. While these methods simply focus on derivatization without addressing the synthesis of the fullerene core structure, a recent development consisted of the catalytic conversion of plastic waste into a magnetic fullerene-based composite, thanks to the key role played by ferrocene, which acted both as a catalyst and magnetic nanoparticle precursor [51].

2.2. Carbon Nano-Onions (CNOs)

CNOs are multi-layered fullerenes that have also attracted attention for potential biomedical uses that range from bioimaging and sensing [6,91] to drug delivery [92], also thanks to a good biocompatibility profile, as shown in vertebrate models [93,94]. Furthermore, for certain applications, they can surpass other carbon nanostructures, as shown for instance by their promising performance as terahertz contrast agents for breast cancer imaging [95].

Their chemical structure similarity to fullerenes poses analogous challenges for their synthesis as described in the previous section. Nevertheless, in this case, there are efforts towards the development of green routes for their production and modification. Tomatoes have been thermally decomposed in alkaline conditions to this end, and lycopene was hypothesized as a possible carbon source [52]. Citric acid was also successfully used as a starting material in a hydrothermal route to CNOs (Figure 2) [53].

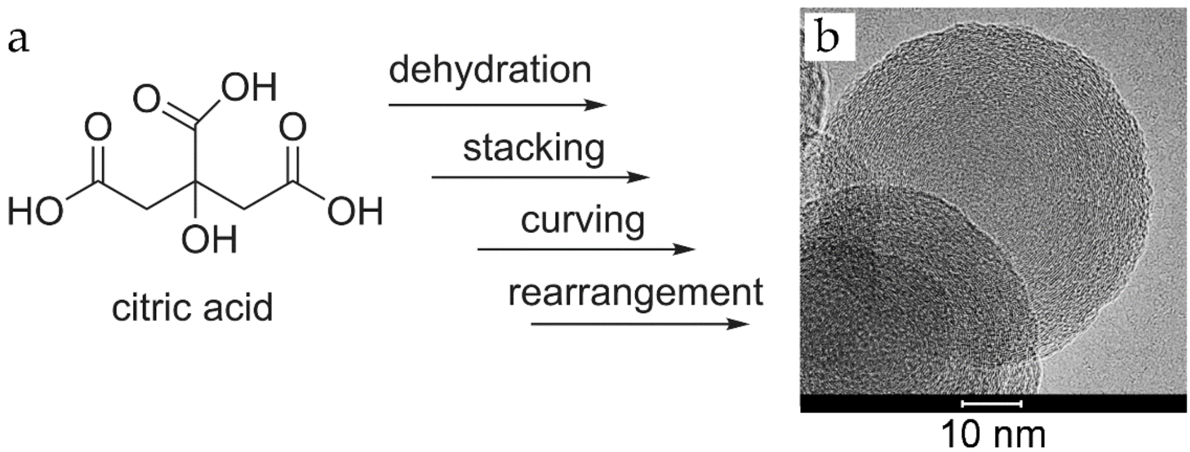

Figure 2. Hydrothermal treatment of citric acid (**a**) yields comprise nano-onions (CNOs), as shown by TEM (**b**). Adapted with permission from [53], Copyright © 2020 Wiley-VCH GmbH.

By contrast, CNO functionalization typically requires organic solvents and harsh conditions at least during the initial steps, for instance, to oxidize defective sites into carboxylic groups for further derivatization [96]. Then, other functionalities can be appended under mild conditions, for instance, as shown for chitosan and poly(vinyl alcohol) to yield composite biomaterials for tissue engineering [97], or for gelatin to yield hydrogels for drug delivery [98], or for protein fibrils to improve CNO biocompatibility [99]. Alternatively, pristine CNOs can be non-covalently functionalized with water-soluble species in aqueous environments, as shown for hyaluronic acid-phospholipid conjugates that allowed the selective targeting of cancer cells for drug delivery [100].

2.3. Carbon Quantum Dots (CQDs)

Carbon quantum dots (CQDs) are quasi-spherical nanoparticles characterized by pronounced luminescent properties, thus very appealing for sensing, and, recently, further morphologies have been attained to fine-tune their luminescent profiles [101], which depend also on the carbon source used [102]. Other applications include photodynamic (antibacterial) therapy [56,103,104], radiolabeled imaging [55], various forms of bioimaging [60,71], and sensing [59–61,69]. They have also been investigated for their antioxidant activity against radical oxygen species (ROS) mediated cell damage [54,64], and as drug delivery agents [105].

Graphene quantum dots (GQDs), which consist of nano-sized graphene monolayers that exhibit quantum confinement, can be produced in a variety of methods, of which the most popular are pyrolysis [69,70] and hydrothermal [57–61,63,64] routes. Other methods that could be carried out at lower temperatures have attracted attention, especially using microwaves [67,68,106], but also ultrasound-assisted approaches [72]. Recently, an electrochemical green approach was developed that employed water and ethanol as solvents [55]. In this case, the dots were also radiolabeled with technetium-99m for imaging purposes, and in vivo experiments overall revealed a good profile in terms of biosafety, although some signs of mutagenic activity were noted [55]. Finally, GQDs were produced by UV-triggered radical polymerization of oxygen-containing aromatic compounds in water for bioimaging, producing just water and carbon dioxide as side-products [107].

A plethora of natural sources have been recently reported for the green synthesis of CQDs. Citric acid and penicillamine underwent pyrolysis to yield nitrogen- and sulfur co-doped CQDs that could detect mercury ions in living cells by means of fluorescence quenching [69]. Concerning plants, and plant derived-materials, various carbon sources have been used. They include fruit parts, such as seed extract [108], flesh [59], peel [61,71], juice [60], and fruit waste [62]. Alternatively, hemicellulose [109] or cellulose, combined with caffeic acid as a green reducing agent [67], or other plant parts, such as Gynostemma plant [54], red cabbage [64], palm-derived powder [110], green tea [63], mint [111], or turmeric [104] leaves, sunflower seeds [112], roasted chickpeas [68], wheat straw [66], soybean residues [113], and sandalwood powder [114]. Some of these carbon sources have been used with the prospect of recycling household kitchen waste, although in line of principle, the same concept could be applied to industrial waste. With this idea in mind, sugarcane bagasse pulp found a second use to be converted in antibacterial CQDs [65].

In the majority of cases, CQDs are used in solution, as they were shown to enter cells by endocytosis and could be tailored to target specific subcellular organelles [108]. However, more research is emerging on their use in composites, for instance to reinforce films for tissue engineering applications [67], to yield luminescent hydrogels [115], or UV-responsive smart (bio)materials [58,116], and antibacterial composites [117].

2.4. Nanodiamonds (NDs)

NDs differ from many of the other carbon nanostructures owing to the presence of a large number of sp^3-hybridized carbon atoms, as the name suggests. However, they do also feature sp^2 carbon atoms [118] and various oxygen-containing functional groups on their surface (Figure 3) that can be exploited for functionalization [119], as recently reviewed [120].

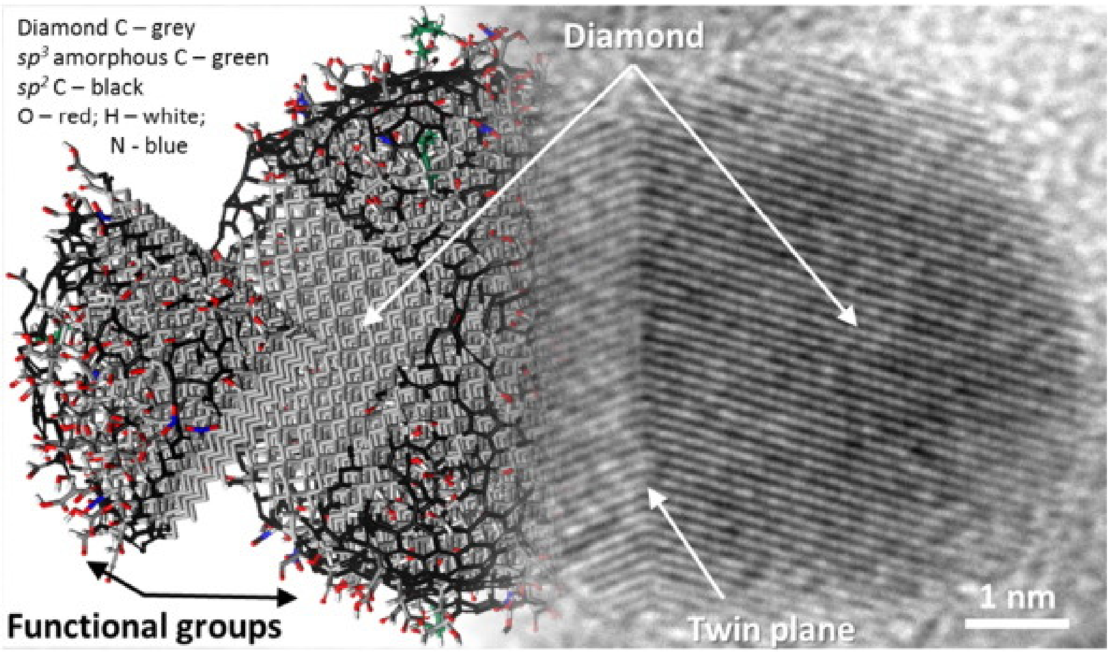

Figure 3. Blended atomistic model (**left**) and high-resolution TEM micrograph (**right**) of a nanodiamond (ND) to show its typical chemical structure. Reprinted from [121], copyright © 2015, with permission from Elsevier.

Their production typically requires high temperatures and pressures to obtain sp^3 hybridization, such as those occurring in detonations. Other methods include chemical vapor deposition and milling of microsized diamonds [9]. Recently, a laser ablation route has been reported as a green alternative due to the possibility to carry it out at ambient temperatures [73].

Due to their low reactivity, functionalization is usually carried out in organic solvents under harsh conditions, or in the gas-phase, and can be promoted by microwaves, plasma, or UV irradiation [120]. Very few reports exist on their functionalization under green conditions. Often, the first step involves ND oxidation by strong-acid treatment [122], to provide functional groups for further derivatization. However, oxidation can also be attained through a green route, using atmospheric-pressure radio-frequency microplasma jet to deliver aqueous oxygen radicals to NDs suspended in water [74]. Then, further functionalization can occur under a variety of classical conditions, for instance to coat NDs with a suitable (bio)polymer for colloidal stability and improved biocompatibility [123]. In the majority of cases, non-environmentally friendly solvents are used, such as dimethylformamide; however, oxidized NDs can be further derivatized also in water [124], or other environmentally-friendly solvents, such as acetone and alcohols, as required for the other reagents, e.g., drugs [125]. Aqueous couplings were performed in this manner to attach a fluorescent protein and CRISPR-Cas9 components for gene editing [122], or to bind polyethylene glycol, and a lanthanide complex for enhanced bioimaging [126].

Alternatively, other useful functional groups for derivatization are alkynes to perform click-chemistry. In one example, NDs were first reacted with glycidol and glycidyl propargyl ether, which both served as reagents and solvents, to then allow the copper-catalyzed click reaction in an aqueous environment with a fluorophore for bioimaging [127]. In a similar approach, the click reaction was performed with a precursor of nitroxide radicals, which could be generated by sonochemical-promoted air oxidation, for redox sensing [128].

Mussel-inspired bioadhesives have also been effectively applied to coat and functionalize NDs in water, so that further molecules could be appended, such as polyethylene glycol polymer for colloidal stability, or DNA for particle tracking (Figure 4) [129]. Another biocompatible coating is mesoporous silica, which can be formed on the surface of NDs in aqueous conditions and allows to include a variety of functional groups, for instance for the convenient grafting of a hydrogel polymer shell and metal nanoparticles for advanced sensing techniques [130].

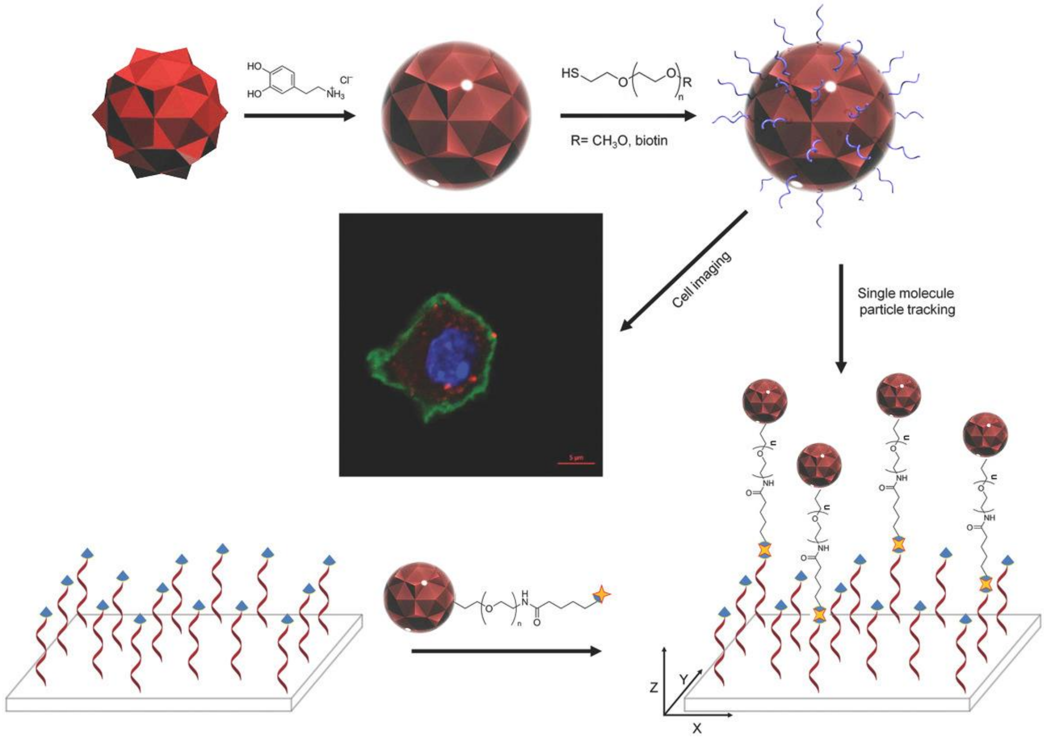

Figure 4. Dopamine can be polymerized in water to coat NDs and provide functional groups for the subsequent anchoring of polymers and biomolecules for imaging and detection. Adapted with permission from [129], copyright © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.

Finally, NDs can be simply used as scaffolds to adsorb other molecular species, as shown for a hydrophobic magnetic-resonance contrast agent that required a mixture of DMSO and water to react with NDs, while the resulting product was water-soluble and could be tested for imaging [131]. They have been proposed as antibacterials [132,133], for regenerative medicine [134], drug delivery [135–137], bioimaging [136,138,139], cancer therapy [137,140,141], theranostics [142,143], and ultrasensitive diagnostics [144]. For many of these applications, they were envisaged to be used in composites [145,146]. Their ability to pass the blood–brain barrier has also attracted attention for targeting the brain, to address existing challenges in the treatment of neurodegenerative diseases [147]. Their rather inert chemical nature renders their functionalization quite challenging, but with the benefit of a good biocompatibility profile [138], depending also on the type of functional groups that they display [148].

2.5. Carbon Nanohorns (CNHs)

Carbon nanohorns (CNHs) or nanocones consist of short cones of sp^2 carbon atoms that aggregate into clusters of ca. 100 nm diameter and can be mainly of two types, i.e., "dahlia-like", when the cones protrude from the aggregate, or "bud-like" when they do not (Figure 5). They are produced by arc-discharge, laser ablation, or joule heating, from graphite [7], although greener alternatives at lower temperatures are continually sought [149]. Similar to the other carbon nanomaterials, they have been proposed for drug delivery [150], sensing [151], theranostics [152], and as components of nanocomposites for phosphoproteomics in cancer diagnosis [153], or for cancer treatment [154], or to yield patches for topical applications on skin [155].

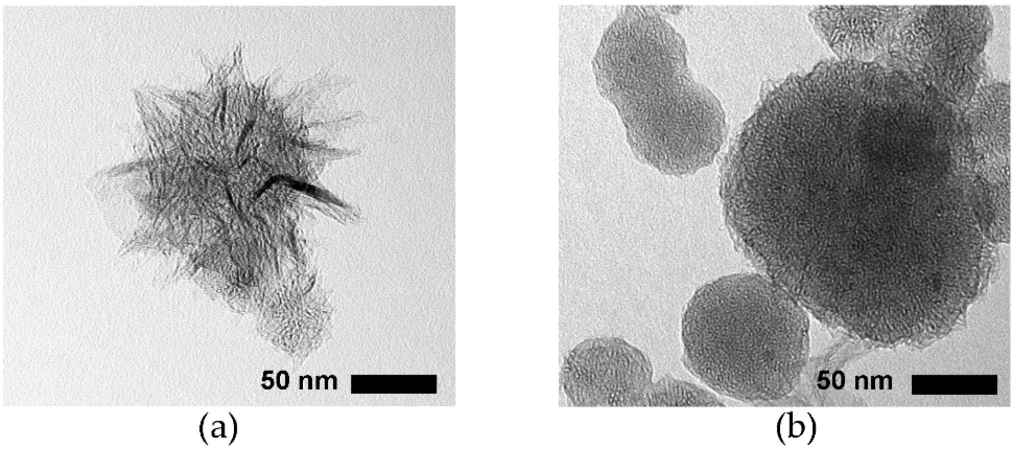

Figure 5. TEM micrographs of (**a**) dahlia-like and (**b**) bud-like carbon nanohorns.

Functionalization is required to avoid further aggregation into larger clusters and ensure homogeneous dispersions in aqueous environments. It is typically carried out similarly to the other nanocarbons, with the most popular route being oxidation (for instance in air at high temperatures) and subsequent coupling to other (bio)molecules in water, as shown with a fluorophore–albumin conjugate to ensure colloidal stability and ease of tracking for bone-tissue regeneration studies [156]. Alternatively, treatment with hydrogen peroxide at 100 °C under UV-irradiation oxidizes CNHs, which then can be purified in water and stabilized with albumin [157], or attached with fluorophore-protein conjugates in aqueous environments, as shown in studies that tracked their cell entrance by endocytosis [75]. However, the most common route to oxidize CNHs is by treatment with nitric acid under mild heating [158], thanks to their high reactivity ensured by the highly curved, thus strained, cone tips. Once carboxylic acid groups have been installed, they can be coupled in aqueous environments to smart fluorophores, which allowed to confirm the endocytic entrance of CNHs into cells [159].

Many other covalent functionalization approaches exist. Among these, 1,3-dipolar cycloaddition of an azomethine ylide, generated in situ from an amino acid and an aldehyde, can be performed in solvent-free conditions in a microwave reactor, for instance to attach oligothiophene to allow Surface-Enhanced Raman Spectroscopy (SERS) imaging [160].

Non-covalent functionalization is also a popular approach. For instance, a simple sonochemical treatment of CNHs with a dye [161] or a natural photosensitizer [162] promoted adsorption onto the CNH surface, thanks to hydrophobic interactions, for combined multimodal imaging, photodynamic, and photothermal treatment of cancer cells, as shown in Figure 6. Similarly, when CNHs were added to albumin under sonication, a stable dispersion could be achieved at physiological conditions [163]. When compared against CNTs, interestingly, CNHs were shown to be more biocompatible due to their reduced ability to adsorb proteins on their surface [163], analogously to what observed for a self-assembling tripeptide [164]. Finally, colloidal stability of CNHs can be ensured also by surfactants, such as the biocompatible pluronic, by simple mixing in water, as envisaged to restore the mechanical integrity of tendon tissues after a sprain [165].

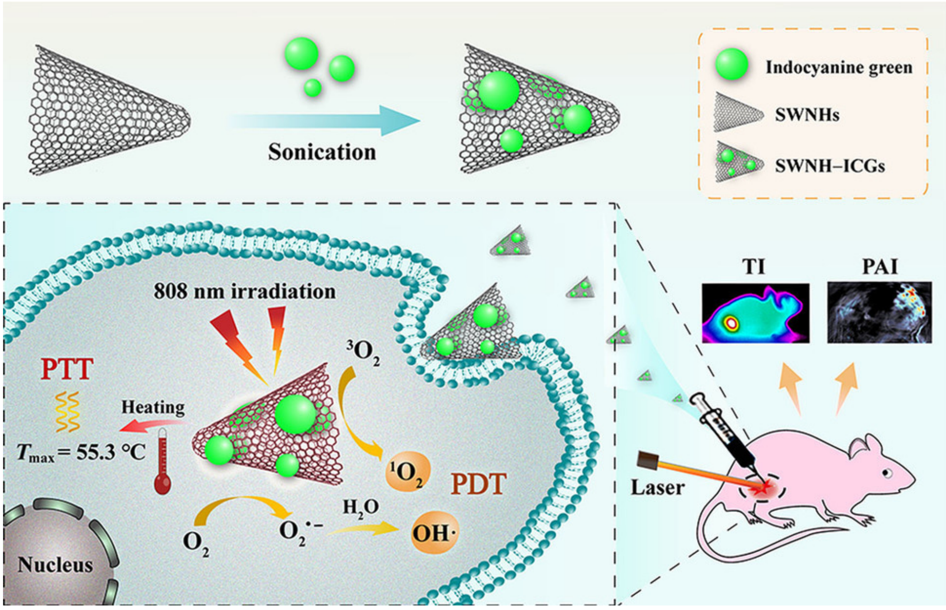

Figure 6. Sonochemical treatment ensures dye adsorption onto CNH surface for theranostics, i.e., multi-modal imaging, photodynamic therapy (PDT), and photothermal therapy (PTT). Reproduced with permission from [161], copyright © 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.

2.6. Carbon Nanotubes (CNTs)

CNTs can be considered as sheets of graphene rolled up in a tube, and comprise mainly single-walled CNTs or multi-walled CNTs, depending on the number of sheets that compose their walls. Similar to the other nanostructures, they have been noted as promising materials to innovate in the biochemical field. However, their morphological similarity to asbestos fibers has posed many barriers for their applications, despite the fact that functionalization can alleviate their toxicity, as recently reviewed [41]. In 2019, CNTs have been added to the ChemSec SIN (Substitute It Now) list, in light of the studies on their toxicity and resistance to biodegradation [166]. This prompted a strong response from the academic community active on CNT research that feared further obstacles to innovation, in which it was noted that toxicity was related to a specific type of CNT, and this class of nanomaterials is very diverse, as the biocompatibility profiles depend on a plethora of factors, which include functionalization and route of administration [167–169].

Indeed, CNTs have shown a unique ability to boost the activity of conductive cells [33], demonstrating an unmissable opportunity to regenerate the cardiac [170] and nerve tissues [34]. Furthermore, their high mechanical resilience and low mass density is promising for orthopedic applications [171]. CNT-coated surfaces effectively stimulated osteogenic differentiation of mesenchymal stem cells, which adhered and spread, with numerous visible focal adhesion and actin stress fibers, as shown in Figure 7 [172]. Besides tissue engineering [173], CNTs have also been proposed to attain antimicrobial and anti-adhesive surfaces for medical applications [174]. Their bioconjugation can serve a variety of innovative applications that span from tissue engineering, to sensing and wearable electronics [175], and, in general, to prepare innovative biomedical electrodes [176]. Their biodegradation is possible, depending also on experimental conditions, route of degradation, and CNT functionalization [43].

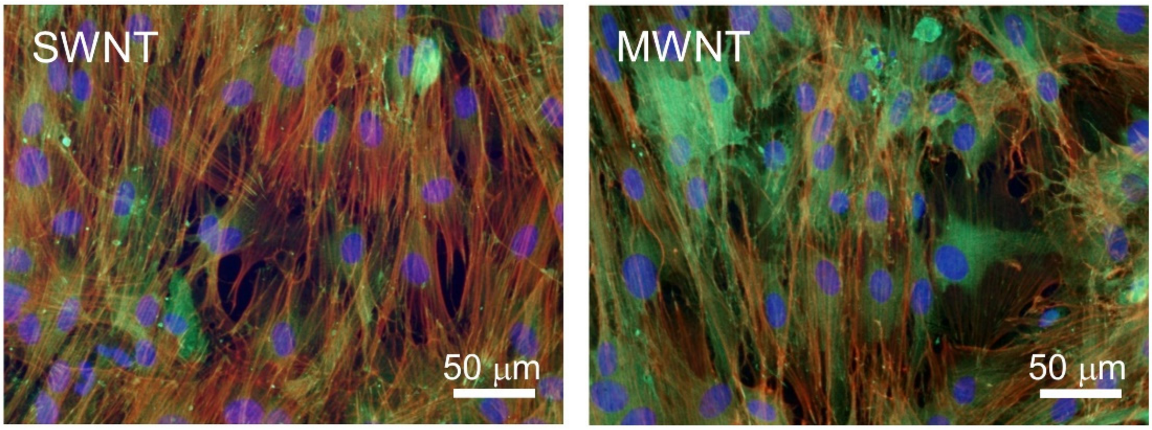

Figure 7. Stem cells (nuclei stained in blue) adhere and spread onto single-walled (SWNT, **left**) or multi-walled (MWNT, **right**) CNT-coated surfaces with multiple focal adhesions (green with vinculin-staining) and actin fibers (red). Reproduced from [172].

As discussed above for other nanostructures, also in the case of CNTs, oxidation is often the first step for their biological application to achieve good dispersibility in water, and this is typically obtained by acid treatment, as shown in a recent study where oxidized CNTs demonstrated antibacterial activity [177]. The process can be carried out also in a microwave oven [178]. However, this kind of treatment requires extensive washings, and greener alternatives include gas-phase methods that use radical oxygen species generated by UV irradiation in air [179]. Once carboxylic acid groups have been installed on CNTs, several subsequent functionalization routes can be undertaken, as needed. For instance, the cationic photosensitizer malachite green could be adsorbed by electrostatic and hydrophobic interactions by simple ultrasonication in water, for antibacterial photodynamic therapy [180]. With an analogous procedure, hyaluronic acid was added to CNTs and the resulting materials were sterilized by gamma irradiation before being used for bone healing [181]. Moreover, without ultrasounds, simple mixing with doxorubicin in phosphate buffered saline solution allowed for the drug adsorption onto CNTs [182]; doxorubicin sustained release by CNTs is indeed a hot topic of research in cancer therapy [183].

Alternatively, the carboxylic acid groups can be covalently coupled to biomolecules in water, as shown for ovalbumin to boost immune response to antigen presentation for vaccine development [178]. With an analogous approach, oxidized CNTs were coupled to dopamine to promote the mineralization with hydroxyapatite, and CNT electronic properties were exploited to achieve directional alignment through agarose gel electrophoresis to form scaffolds with collagen, which promoted the healing of bone defects in vivo [184].

Non-covalent CNT functionalization is also a popular route, as it does not disrupt their electronic properties. Use of ultrasounds promoted the wrapping of CNTs by polyethylene glycol-pyrene polymer to achieve stable dispersions to induce apoptosis of colon cancer cells by applying nanosecond electric pulses, which affected calcium flux within cells [185]. Simple mixing of CNTs with cationic polyamidoamine polymer and anionic dsRNA, with ultrasonication at room temperature, provided coated CNTs for gene knockdown interventions [186]. Similarly, sonication of CNTs with DNA in saline solutions, followed by purification using polymers, was effective to yield dispersible CNTs that showed very good short-term and long-term biocompatibility in vivo [187]. DNA–CNT complexes were also used in hydrogel composites with silica nanoparticles to deliver doxorubicin [188]. When dispersed with Triton within a glycol-chitosan hydrogel, CNTs promoted cell migration and recruitment, with potential applications in wound healing [189]. Conductive composites for potential applications in sensing were obtained by mixing CNTs with soy lecithin, natural rubber, and the green solvent methyl isobutyl ketone in a homogenizer at high pressure [190].

2.7. Graphene-Based Materials

The class of graphene-based materials is vast and diverse, thus it is important to be aware of the specific type of structure under study, and how it may differ relative to existing literature on the topic [191]. Graphene has captured scientists' imagination for a variety of uses in medicine, yet there are still unsolved challenges to its wide implementation on a global industrial scale to widely reach the market, although steady progress is being made in this direction [192]. Among the many applications, those related to antibacterial properties are highly studied [193]. The unique properties due to the 2D nature of graphene-based materials are of particular importance for uses in sensing [194]. These materials have been widely studied for their biocompatibility and the data gathered thus far is promising, although, given the wide diversity of graphene-based materials, it is desirable to move from descriptive to predictive toxicology [5]. In particular, formation of a biomolecular corona on graphene-based materials and its consequences on biodistribution and cytocompatibility has been recently reviewed [39].

Graphene can be produced in a variety of ways, of which the most popular include graphite exfoliation in the presence of various dispersants (Figure 8). However, to ensure good water dispersibility, graphene is typically oxidized to graphene oxide (GO), in a process for which green alternatives are continually sought [195]. In particular, electrochemical oxidation of graphite in acidic water was efficient within seconds to yield GO-based conductive materials [76]. The process could be further enhanced by exploiting synergy with photochemistry [77].

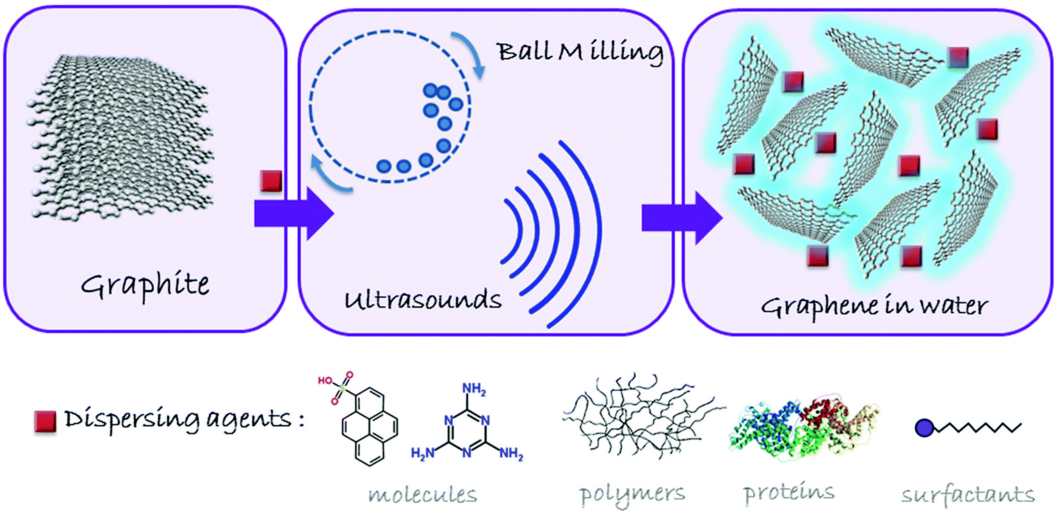

Figure 8. Graphene dispersed in water can be obtained from graphite through exfoliation with a variety of dispersing agents. Reproduced from [192], published by the Royal Society of Chemistry.

GO is often reduced for enhanced electronic properties, and quite a few green approaches for this step have been recently reported. For example, GO was efficiently reduced by natural polysaccharides extracted from an edible mushroom to yield nanosheets that displayed good biocompatibility up to 0.1 mg/mL [78]. The amino acid cysteine was also effective at reducing GO in ethanol/water solutions with a sonochemical treatment, to yield rGO that was then embedded in a hydrogel for drug delivery [79]. Ascorbic acid provided another example of green reductant for GO to yield nanostructures that were investigated for applications in neuroscience [80]. Once GO or rGO is produced, the material can be further functionalized as described above for the other oxidized carbon nanomorphologies, covalently or non-covalently, as shown for instance for the bioconjugation of a peptide that benefited from enhanced antibacterial activity and reduced hemolytic effects [196]. Green routes towards inclusion of GO into (bio)composites are also receiving attention [197].

3. Conclusions

Carbon nanomaterials come in different shapes and sizes, each one with its own peculiar opportunities and challenges to innovate in nanomedicine. Over the last decades, they have been widely investigated for a variety of applications as described in this review, and in recent years, more attention has been paid to green routes towards their production and modification.

Among the various approaches described in this review, the use of microwaves and photochemistry are certainly among the most promising strategies that, in line of principle, could be extended further to many other different types of chemical functionalization. At present, the use UV-generated radicals or UV-H_2O_2 mediated oxidations appears particularly attractive, since these are convenient oxidation alternatives to more traditional routes that employ strong acids. Benefits are varied. First, the reaction can be carried out in portable devices with UV-lamps that are widely available. Second, if the reaction is performed in the gas-phase, there will be no liquid or solid waste; hence, no need for extensive washings for product purification. Alternatively, if the reaction is performed in the liquid phase with hydrogen peroxide, there will be benign byproducts. Third, UV-promoted oxidation in the gas-phase was shown to be effective also in preserving the macroscopic morphology of the materials, such as the case of CNT fibers. Electrochemistry is another very promising approach; however, it requires knowledge and equipment that may not be available to all.

In many cases, carbon nanomaterials' limited solubility in polar solvents and reduced reaction yields in green conditions drive scientists to opt, in practice, for the non-environmentally friendly protocols. However, the hope is that as more literature is gathered on this interesting topic, the community of scientists willing to adopt and develop greener routes will widen significantly to fully unlock the potential of these innovative materials for the maximum benefit of society and the environment.

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