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Application of carbon allotropes composites for targeted cancer therapy: A review

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ABSTRACT

In recent years, various drug carrier nanomaterials have been investigated to improve drug delivery systems in cancer treatment. However, an ongoing requirement exists for more beneficial therapeutic materials, yielding rapid clearance, high capacity for reducing systemic toxicity via specific-tumor targeting, and superior drug solubility. Given that, carbon allotropes, including Active Carbon (AC), carbon nanotubes (CNTs), graphene and graphene oxides (GOs), nanodiamonds (NDs), fullerenes, carbon nanohorns, porous carbons, and carbon dots, have been studied owing to their high thermal conductivity, rigid structure, flexibility for modification and functionalization, adequate surface-to-volume ratio, and high biocompatibility. This review aims to overview recent advances in applying different carbon allotrope composites in drug delivery-based cancer therapy systems.

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1. Introduction

Cancer is a non-communicable disease recognized as the most worldwide deadly disease in humans, responsible for more than 9.6×10^6

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mortalities in 2018 [1]. The common therapeutic strategies could not accomplish a beneficial cure for cancer [2, 3]. Bray et al. [4] believe that cancer is the main hurdle in retracting from an anticipated growth of life expectancy in the 21st century. However, consuming less than 5% support funding regarding the fundamental studies of cancer shows that

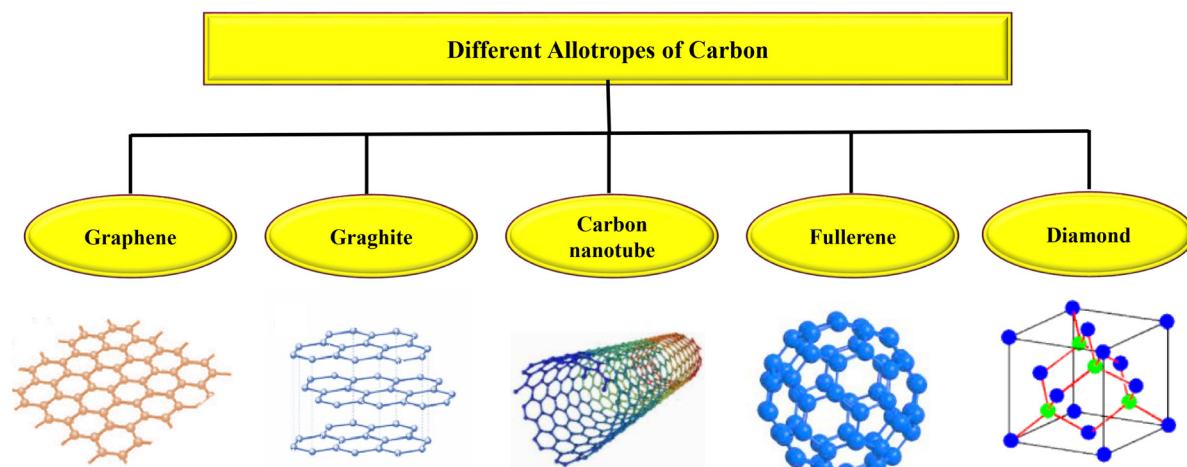


Fig. 1. The schematic illustration of the most common carbon allotropes.

the critical objective for cancer curing is impending.

The accumulation of somatic mutations in a normal cell progeny leads to an evolutionary process named cancer, which causes a discerning growth benefit and unrestrained cell propagation. The most critical cancers in humans are caused by epithelial tissues of the colon, breast, lung, prostate, stomach, and skin [5, 6].

Although there are enormous developments in the cancer disease understanding at the molecular scale, the high tumor heterogeneity and diversity limit to achieve modern treatment methods, which is a major challenge that should be addressed appropriately [7]. In addition, cancer cells are distinguished from normal cells by their different metabolic and genetic profiles. As a result, the development of novel anticancer handling approaches, which target the alterations of tumor cells, is another main challenge in pharmacology [8, 9]. There are many tumor handling strategies, including immunotherapy, chemotherapy, radiation, and surgery [10]. While the best operative treatment for metastatic cancers is chemotherapy [11], the potential of cancer cells to multidrug resistance, the concurrent resistance of tumor cells to altered drugs, is an important obstruction to chemotherapy success. In addition, their various side effects are defined mainly by their toxicity impacts, cancer repetition, and healthy cell-damaging due to their inability to target tumor locations appropriately [12, 13].

Thus, cancer investigation pursues treatments to minimize these undesirable side effects, touching to the excellent capable, innovative therapies, for example, nanomedicine and drug delivery [14].

Unique medication delivery methods targeted particularly to cancer cells can be used to reduce the detrimental and hazardous cytotoxicity on healthy organs and destroy malignant cells with minimal injury to normal tissue. In addition, using the right drug delivery system can help patients receive faster and better treatment [15]. Thus, finding innovative and effective drug delivery methods is one of the major challenges that academics are focusing on.

The present review intends to provide an overview of modern theragnostic applications of carbon allotropes and deliver a complete comparison concerning nanocarbon characteristics and their effects on theragnostic applications, particularly in drug delivery targeting cancer cells. Firstly, the different allotropes of carbon associated with their cancer theragnostic applications are introduced here. Then, their chemical and physical properties are explained, along with their production and surface functionalization methods. Finally, the theragnostic applications of different carbon allotropes associated with *in vivo* and *in vitro* systems are demonstrated by emphasizing the investigated biosystems and tumor drug delivery techniques.

2. Carbon allotropes-based drug delivery carriers for cancer therapy

Engineering, technology, and science are fused in the nanotechnology field, aiming to investigate, create, and use nanoparticles, which means any particle of materials with a dimension around 1-1000 nm [16]. The measurable physico-chemico-biological features of particles are granted by nanosize. As a result, their performance is improved in comparison with bulk materials. In concern to medicine, nanotechnology includes nanoparticle applications to improve new therapies and increase current methods. For example, the nanotechnology field has the incredible ability to play an important role in detecting, treating, and preventing cancer [10, 17].

Recently, materials chemistry is amid the fastest-growing fields in science and attains great worldwide attention. This severely emerging field contains either modifying the preexisting materials or producing new ones, chemically and/or physically, to develop their characterizations and applicability. For example, carbon nanomaterials (CNMs) are attractive because their unique properties involve large surface areas, tunable pore structures, rigid structures, post-chemical modifying, high thermal and electrical conductivity, wear and thermal resistance, chemical stability, and low friction coefficient [2, 18, 19]. Carbon nanoallotropes have great potential for filling the gap between organic molecules and carbon materials [20]. Allotropes of carbon have great diversity in size and shape. Based on the morphology, carbon nanoallotropes are categorized into two classes, including nanostructures with inner cavities (carbon nanotubes (CNTs) [21] and fullerenes [22]) and not bearing inner voids (graphene [23], carbon dots (CDs) [24], and carbon nano onions (CNOs)). In addition to graphene nanoribbons [25], graphene oxides [26], and nanodiamonds [27], some macro and micro-structures are formed by carbon materials, for instance, 3-dimensional (D) microspheres, 2D films, and 1D nanowires.

Figure 1 shows the schematic of natural carbon allotropes (graphite and diamond) and synthetic examples (graphene, nanotubes, and fullerenes). Due to their distinctive chemical and physical properties, nano carbons remain high-attractive materials in many applications, including photovoltaics to sensing, optoelectronics, electronics, bioimaging, and therapeutics [28, 29].

The diagnostic and therapeutic applications of nanocarbons are intensively investigated as superb biosensors, capable fluorescent nano labels for imaging tissues and cells, operational photothermal nano reagents to tumor therapy, gene carriers, and being used in different types

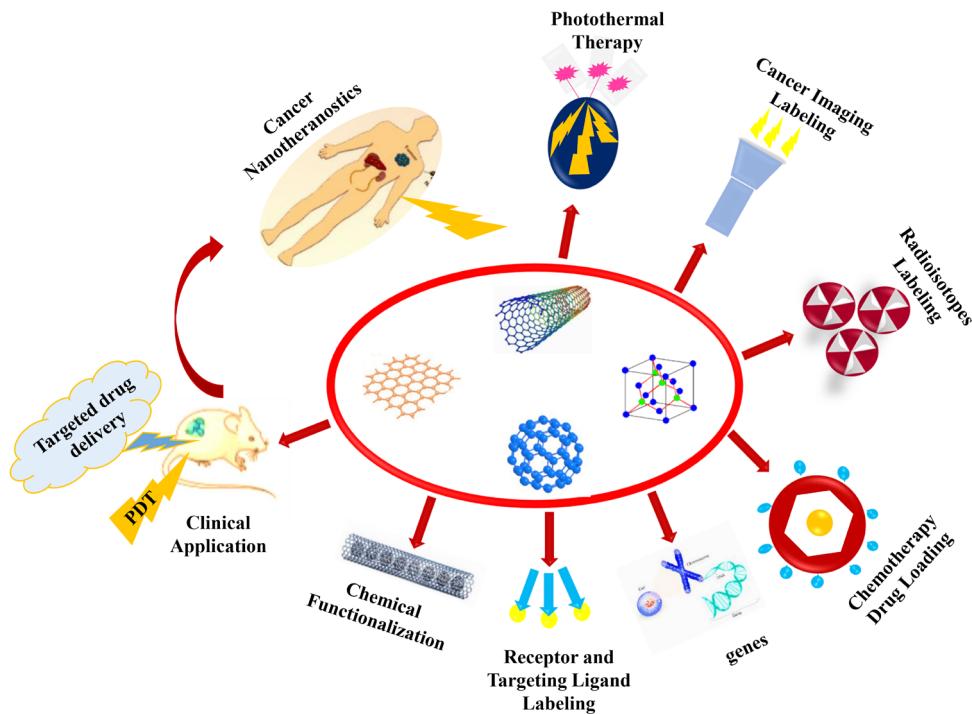


Fig. 2. Schematic diagram of using carbon allotropes in cancer theranostics.

of drug delivery systems [30, 31], particularly *in vivo* targeting cancer cells [28, 32, 33]. Among these, because of the unique physicochemical properties of nanostructured carbon materials such as graphene, nanodiamonds, fullerenes, and CNTs, they are highly investigated to tumor theranostics from the various aspects, for example, their engineering possibility for practical therapeutics matters and multi-function diagnostics [34, 35]. Within a live body, nanoparticles comprising carbon allotropes have a distinct behavior, distribution pathway, and toxicity [36, 37]. Some of these carbon allotropes show extremely photothermal impacts due to their capability to absorb the near-infrared radiation (NIR), a feature that can be applied to the *in situ* killing of cancer cells in a short time [38, 39]. Figure 2 shows the schematic diagram of using carbon allotropes in cancer theranostics.

2.1. Active Carbon (AC)

Well-known as charcoal, AC is one of the prominent participants in the carbon family. The structure of AC is amorphous and chemically stable. It is prepared from various carbonaceous resources, for instance, coal, wood, bamboo, and coconut shells [40]. This type of nanocarbon is a more interesting material for medical applications such as a therapeutic function for treating severe toxicity and/or overdoses through directly consumed drugs, such as acetaminophen and diethylcarbamazine, and even in acute poisoning cases. It can also be activated in drug delivery sets. AC could be a great alternative to carrier drugs in cancer therapeutic agents [41].

2.2. Carbon nanotubes (CNTs)

CNTs, attracting much attention during the last decade, contain unified rolling cylinders made of graphene sheets. These materials exhibit supreme chemical, mechanical, and physical characterizations [42, 43]. There are two classes of CNTs, including multiwalled (MWNTs) and single-walled (SWNTs) based on their graphene layer (that constitutes only one nanotube) number [44]. The rolled organization of graphene sheet layers could be formed as different-layered from single to multiple-layered, which are denoted as numeral-walled nanotubes (NWCNTs), for example, multi- (MWNTs), triple- (TWCNTs), double- (DWCNTs), or single-walled nanotubes (SWNTs) [42]. Figure 3 shows four major types of CNTs.

Functionalized CNTs have demonstrated excellent biocompatibility, making them attractive choices for anticancer treatment and diagnostic drug delivery [45]. For example, a novel nanoformulation including platinum nanoparticles (NPs) maintained on polybenzimidazole (PBI) functionalized polymers and MWCNTs were produced for cancer treatment [46]. This nanosystem exhibited potent inhibition on the epithelial-mesenchymal transition and cell cycle biomarkers of cancer stem cells, as well as specific cytotoxicity on breast cancer stem cells, though not on adult stem cells, according to quantitative gene expression assessments [46]. Singhai et al. [47] used hyaluronic acid and α -Tocopherol succinate to functionalize MWCNTs and then loaded them with Doxorubicin hydrochloride (DOX) to achieve better cellular positioning and appropriately targeted CD44 receptor overexpressing triple-negative breast cancer cells (MDA-MB-231). The cellular absorption of the product was noteworthy, with strong proliferation inhibitory action and a significant overall apoptotic rate. Hyaluronic acid and DOX were employed as CD44 receptor targeting ligands and chemotherapeutic agents, respectively, in this nanoformulation, and α -Tocopherol succinate was chosen because of its synergistic benefits. These chemicals exhibited the appropriate synergistic effects and were safe enough to be used in targeted anticancer treatment [47].

2.3. Graphene and graphene oxide

Graphene contains sp^2 -bonded carbon atoms located in a two-dimension (2D) layer, in which each carbon atom fused to three carbons with a bond angle of 120 and arranged six-atom rings to construct a honeycomb network of one-atom thickness [48-50]. The sp^3 -bonded graphene membranes are made up of two or three layers of known and novel *in silico*-designed carbon bulk architectures, with hydrogen passivated surfaces on both, one, or none of the surfaces. Many possible stable configurations of sp^3 -bonded membranes exhibit varied electronic characteristics and transverse and longitudinal mechanical behaviors. In addition, carbon membranes rich in sp^3 bonds demonstrate mechanical qualities and optimum breaking strengths [51].

The graphene biomedical applications, such as drug delivery, were quickly developed a few years ago due to unique features of graphene, for example, noble biocompatibility, 2D planar structure, mechanical and chemical stability, large surface area, and excellent conductivity. As

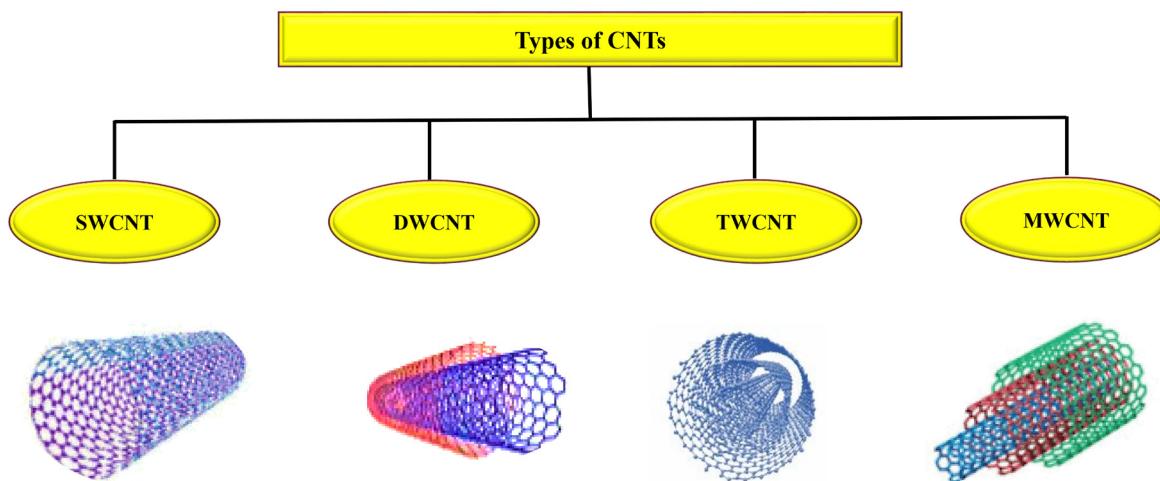


Fig. 3. The schematic of major types of carbon nanotubes.

a result, graphene-based materials have been widely investigated as high adequate biomaterials in biomedical applications, for instance, delivering a broad therapeutic series and designing innovative drug delivery structures [52].

Graphene oxide (GO), the main derivative of graphene, has great properties, including promising optical activity, cost-effectiveness, low toxicity, and good water solubility, making it a suitable candidate for bio probe developments [52]. Due to their typically large surface area, GO and GO-based nanoparticles can be used for combination chemotherapy and dual-drug delivery [53]. Supramolecular hydrogels of injectable graphene/GO composite were improved by Hu et al., aiming to carry anti-tumor drugs. GO and its reduced derivative (RGO) were stabilized in solution using Pluronic F-127. The storage modulus related to composite hydrogels of RGO or GO was higher than the native hydrogel, which gradually damaged and was unsteady in solution. The solubility of the water-insoluble anticancer drug camptothecin (CPT) in Pluronic F-127 solution, particularly the large drug-loaded sample, was improved by GO or RGO. In addition, the hydrogel of RGO or GO composite showed great potential to superior control and milder drug release (to both DXR and CPT) than native hydrogel [54].

There are few published studies concerning the anticancer activity of graphene or GO [55-57]. In this regard, the anticancer behavior studies of GO-hypocretin A in an aqueous media revealed its superior activity to free hypocretin [58]. A hybrid of GO-TiO₂ led to major promotion in the activity of caspase-3 involving apoptotic death [59]. Furthermore, the hybrid exhibited exceptional photodynamic activity as an anticancer due to the lack of dark cytotoxicity [60]. Wang et al. [60] and Hu et al. [59] established the double functional graphene quantum dots as carriers for anticancer drug targeting and savories for activating DNA cleavage, which was useful to cancer therapy. It was illustrated that polyethylene glycolated GO conjugated with transferrin as a proficient nanovector could target brain cancers *in vivo* and *in vitro* as an anticancer drug delivery system [61]. Gurunathan et al. [58] revealed that GO-CONH-Schiff base composite, as a nanostructured pH-sensitive antitumor drug, could be operated as a carrier of drug delivery and the inhibitor of cancer. Jagiello et al. [62] fabricated the composites RGO and GO with NPs such as AuNPs, AgNPs, Ag₂O, and TiO₂. These compounds displayed high vibrant surface regions and enabled adhesion to inorganic and organic molecules, which were proper to be applied in different biomedical applications involving anticancer therapy, bioimaging, or tissue regeneration.

Moreover, Su et al. [63] summarized that modifying the GO surface remarkably improved its physicochemical features, providing the appli-

cant with a vaccine carrier and activating humoral and cellular immunity. The functionalized GO as a capable substrate to cancer treatment and chemotherapeutic drug delivery was deliberated by Gupta [64]. Generally, the studies indicate that new attempts in graphene and GO are concentrated in modifications, fabrications, and improvement of their characterizations. They were reviewed by Farjadian et al. [55], and the variation of oxidation degrees can change GO interactions with proteins.

2.4. Nanodiamonds

A new participant in the carbon nanoparticle family, nanodiamonds (NDs), is more attracted to biomedicine due to their superb chemical and physical features [65, 66]. Since their initial studies in Russia in 1960, nanodiamonds have extended global consideration because of their simplistic surface modification involving excellent biocompatibility and bio-conjugation, the small size of the prime particle (about 4-5 nm) having narrow size distribution, and economic large-amount production. They also appealed a lot of technological and scientific attention due to their distinctive optical, chemical, structural, mechanical, and biological properties [67]. Having a diameter of ~5 nm, along with highly tailorable surface chemistry and low cell toxicity, rendered them to be exciting materials for improving drug delivery structures summarized by Mochalin et al. [68]. NDs integrate numerous features, such as scalability, variety of impending conjugates, biocompatibility, and surface geometries, which facilitate the high-affinity release of therapeutics. NDs can also provide wide-ranging therapeutics, for instance, nucleic acids, proteins, and small molecules [67, 69]. *In vitro* biocompatibility of ND has been discovered by a wide series of assays [70, 71]. Additionally, the sides existing on the surface of ND possess burden characters that facilitate effective water-binding for sustained and dispersibility therapeutic release [72-74].

An apoptosis-making drug, DOX, extensively employed in chemotherapy, was reversibly and effectively anchored over the nanodiamonds (NDs, 2-8 nm) and hosted in alive cells. The observation of feasible and genetic interrogation research of DOX-functionalized ND composite confirmed this material applies to as a platform transport technology for a broad nanoscale medicine modality and multitude of therapeutic molecules [75].

The ND-C60 composite obtained from crushing nanodiamond (ND) with dry powder of C60 quickly adsorbed and oxidized organic contaminants using photogenerated ROS. Moreover, the photodynamic tumor therapy studies showed that ND-C60 without apparent toxicity could be internalized by tumor cells and made cell apoptosis. Besides, the treat-

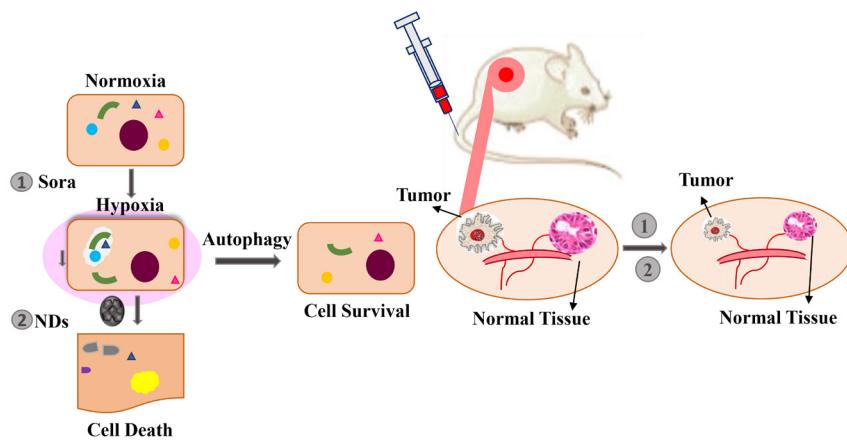


Fig. 4. Systematic diagram showing the experimental studies of NDs and Sora composite impacts on hypoxic tumor cells and the suggested mechanism.

ment of ND-C60 with mice cells bearing tumors along with light irradiation extended survival time by reducing cancer [22].

Furthermore, the study of NDs impacts on HIF activities and lysosomal agents displayed that NDs, in contrast to Baf A, successfully triggered autophagic flux obstruction without harming the lysosomal activities [76]. Besides, a combined system of NDs and Sorafenib, an anti-angiogenic drug, inhibited cancer growth via a synergistic impact. A suggested mechanism exhibited that the autophagic flux was blocked by NDs through a distinctive instrument from lysosomotropic reagents and might function as a targeted agent for tumor therapy while blending with oxygen scarcity [77]. Figure 4 illustrates experimental studies of NDs and Sorafenib (Sora) composite impacts on hypoxic tumor cells and the suggested mechanism.

2.5. Fullerene

After diamond and graphite, fullerene is the third allotrope of carbon, known as zero-dimensional nanostructure, which is a suitable and superb alternative to numerous applications in various fields due to its exclusive structural and electronic properties. After discovering C60 in 1985, this kind of nanostructures rapidly improved because of their remarkable physicochemical features [78]. Their most notable characters are the capacity to reversibly take several electrons, great thermal stability, large surface area, and wide absorption ranges [79, 80].

C60 is the most important member of fullerenes. This fullerene demonstrates both distinctive antioxidant behavior, biological activity, and physicochemical features, and has an important serving potential to be a nanocarrier for delivering drugs to tumor cells [81]. In nanotechnology, the biomedical application of C60 fullerene has recently attracted more attention due to its multipurpose biological activity and unique structure. The exploitation of double functional C60 as a photosensitizer demonstrated that C60 nano complexes showed an increased effect on chemotherapy of drugs, such as DOX, into leukemic cells of humans. It was also established that this strategy could be transferred to a potent alternative for delivering anticancer drugs, for instance, Berberine. In addition, the blend of photo- and chemo-dynamic treatments with drug nano formulated C60 opened promising synergistic strategies to drug delivery for tumor treatment [82].

Due to the low solubility in inorganic and organic solvents, original forms of non-modified carbon nanostructures (CNs) cannot be used in various fields [83]. The intermolecular van der Waals interactions between these materials cause their aggregation. Thus, functionalizing CNs is needed to increase their solubility and expand their applications in numerous fields [84].

The increased fullerene solubility by modifying chemical methods, such as anchoring hydroxyl or amino groups, leads to the broadly applying of C60 in the biomedical areas [85]. Naim et al. (1992) [86] reported

the first hydroxylated fullerene C60(OH)n afforded through the heating of C60/C70 with the excess KOH in toluene under reduced pressure. Chiang et al. [87] obtained C60(-OCOR)x(OH)y through the electrophilic reaction of C60 with NO2BF4 using an aromatic acid mediator (RCOOH). C60 was also directly modified with 18 carboxylic functions and 24-26 hydroxyl functions. The highly water-soluble derivatives of malonic acid used to synthesize dendron fullerene and an aqueous NaOH and tetrabutylammonium hydroxide (TBAH) were applied to produce the multi-hydroxylated C60 [88, 89]. Moreover, Hu et al. [90] covalently modified C60 with an amino group to synthesize a series of folacin- and amino-fullerenes soluble in water.

There is evidence that the solubility improving C60 intensely affects the toxicological and physicochemical features of these compounds, therefore makes difficulties in the estimation of their therapeutic potential and toxicity. The in vitro studies concerning the impacts of two fullerenes (1 and 2) on the gene expression in the MCF7 cell line of humans showed that these compounds had null and cytotoxic impacts. The mechanisms of varied behaviors related to the many fullerene derivatives have still been unidentified in alive cells. The reactive oxygen species (ROS) generated along with the light-absorbing potential of fullerene (C60) was extensively investigated for cancer therapy and the water treatment of photosensitizer [22]. Fullerene displays superb capability to tumor therapy. However, the fullerene-lasting deposition and OH· generation have not been thoroughly explained in the literature. The mixed solutions of silk fibroin, water-soluble fullerene (SF-WSF), lead to fairly altered in vitro fullerene performance. It is established that SF can produce promising consequences, including 1) owing to hastening the fullerene degradation by SF, causing low deposition, and 2) the OH· of durable deposited water-soluble fullerene organization is scavenged in the attendance of SF. Hence, SF delivers an opportunity to OH· scavenged, which may be accessible for inhalation and intratracheal instillation applications. Researchers should consider the suitable mixture of different properties for nano n composites, including SF and fullerene, which would be favorable to reduce tissue injury and suppress the oxidative stress using the compounds. Moreover, the perfect separation of nanocomposite biomaterial varied property plays an essential role in updating new applications [91, 92]. The schematic diagram of some derivatives of fullerene applied to cancer therapy and diagnosis is illustrated in Figure 5 [93].

2.5.1. Structures of fullerenes 1 and 2

Proposing to design a smart carrier of drug based on the trimethyl chitosan (TMC) and fullerene, Maleki et al. [94] performed a simulation of molecular dynamics (MD). They found that the functionalized fullerene with carboxyl molecule and spending TMC might increase anticancer drugs such as PAX and DOX and biocompatibility, and reduce drug

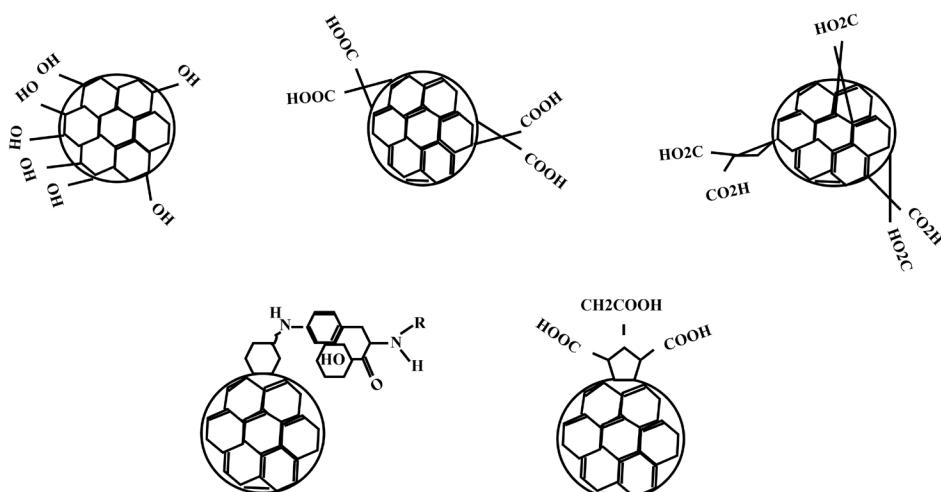


Fig. 5. The schematic diagram of some derivatives of fullerene applied to cancer therapy and diagnosis. 1) Gadolinium endohedral metallofullerene $\text{Gd}@\text{C}_{60}(\text{OH})_{24}$; 2) Carboxyfullerene $\text{C}_{60}(\text{C}(\text{COOH})_2)_2$; 3) C_3 (e,e,e-tris-malonic acid fullerene derivative); 4) Bucky amino acid (Baa); 5) Amino acid-type fullerene derivative.

side effects. Numerous anticancer drugs, such as PAX and DOX, can bring a set of side impacts through non-tumor cell damaging.

Lin et al. [95] designed and prepared a metal-organic photodynamic framework (PHF@ZIF-8). The PHF was loaded in the ZIF-8 to prevent aggregation and solve the solubility problems of fullerenes as photosensitizers. It was reported that the PHF@ZIF-8, under laser irradiation with 448 nm spectrum, showed great therapeutic affectivity, indicating the capability of this compound application to tumor treatment. Jiang et al. [96] prepared and determined a novel set of C60 derivatives with great water-solubility, using ^1H NMR, FTIR, ^{13}C NMR, TGA, SEM, and UV-Vis. Since materials based on fullerene-glycine derivative are bioactive, the cell apoptosis and mortality were enlarged with enhancing the concentration of fullerene-glycine derivative in comparison to fullerene complex. Altogether, these results show that the new, extreme derivatives containing water-soluble C60 can be used for tumor therapy. Guan et al. [97] effectively synthesized the UCNP-PEG-FA/PC70 nanocomposite as a targeted theranostic platform and/or a NIR light-triggered for *in vitro*, *in vivo*, and PDT guided trimodal imaging. The following are benefits associated with improving nanocomposites of UCNP-PEG-FA/PC70. (1) Upon irradiation of NIR, UCNP can make the conversion of NIR to UV-to-visible light for successfully activating PC70, which yields O_2 to kill cancer cells under poor oxygen environments, (2) integrating three imaging techniques (FL/UCL/MR) into one set aims to afford the corresponding data of cancer directing treatment and careful diagnosis, and (3) leading superior retention and permeability impacts through passive targeting of folate activated with the PEG, which increases multifunctional nanoparticle accumulations in cancer. Notably, the produced UCNP-PEG-FA/PC70 might answer the two PDT blockage difficulties, including oxygen-poor microenvironment and depth-penetrated limitation. These outcomes emphasize the UCNP-PEG-FA/PC70 ability as multiple theranostic reagents to cancer PDT-guided imaging and a favorable alternative to overcome the drawback of deeply cancerous tissues existing PDT agents under complete deprivation of oxygen (hypoxic) conditions. Li et al. [98] used (PEG)-modified poly(amidoamine) dendrimers to develop supramolecular nanocomposites based on fullerene-dendrimer and reported that these nanoparticles were non-toxic and superbly water-soluble.

2.6. Carbon Nanohorns

A graphene-based nanostructure in horn shape, single-walled carbon nanohorns (SWCNHs), could be appropriate nanosystems to drug delivery targeting through assembly with multipurpose properties of an agent. These materials are simply prepared and modified to obtain the non-toxicological impacts and favorite physicochemical features. Some reports

are referring *in vivo* administration of these properties [99].

From a topological and morphological viewpoint, CNH contains a narrowed front-tip unit (the angle of the cone is 120° , and its critical diameter and length are 2–5 nm and 40–50 in size, respectively) collected of carbon atoms with sp^2 spin organized in five pentagons (found in F as well). CNT-like hexagon ramparts can also be formed by arranging a sixth pentagon around the axis [100]. Moreover, heptagons exist in the axis long to deliberate the usual CNH chemistry and counteract the variation associated with curving pentagons [101].

Depending on the morphologies formed from aggregating CNH assembles, some of these compounds are seed-, bud- or dahlia-like [102]. Notably, the dahlia-like type of CNH, commonly used in nano-oncology applications, has a spherical morphology, and its diameter changes in the range of 80–100 nm. This CNH collected almost 2000 tube-shaped units [103, 104].

Having properties such as “enriched permeation and retention” (EPR) impacts, SWCNHs, holes, high surface areas, lower intrinsic cytotoxicity, SWCNHs are attractive for use as delivery motors to successfully transport different molecules, for example drugs, contrast agent, photosensitizers, fullerene, small interfering RNA (siRNA), and proteins. Despite these favorable applications and features, the uses of oxSWCNHs as carriers of drugs have been limited due to their low dispersibility, which should be addressed appropriately [101].

Modification of CNHs could increase their aqueous solubility and extend their biological applications, such as photodynamic therapy, biosensors, and drug delivery sets (DDSs). It is reported that the dispersibility of oxSWCNHs in water is made using non-covalent and covalent functionalization. Among them, non-covalent modifications are easy and can reserve the natural features of oxSWCNHs. In addition, a natural polysaccharide, sodium alginate (SA), improves the biocompatibility and dispersibility of carbon nanomaterials through non-covalent functionalization [105].

Despite CNTs that forms large bundles, spherical conjugated SWCNHs only aggregate with small size, having < 100 nm in diameter. Hence, the SWCNHs minor size is extra appropriate in the physiological media to succeed a greater cell uptake and the efficacy of targeted delivery into the cancer cells. For instance, Ajimi et al. [106] synthesized nanocarriers of SWCNHs for cisplatin (CDDP) using a nanoprecipitation method. The efficiency of CDDP loading on SWCNHs can be nearly 46%, and the percentages of CDDP drug release for different solvents were 100–60% for water and dimethylformamide, respectively. Furthermore, its anticancer efficiency was enhanced by almost 4–6 folds in comparison to free CDDP drugs. *In vitro* delivery research of CDDP-loaded SWCNHs in lung tumor cells of humans using NCI- H460 as a model demon-

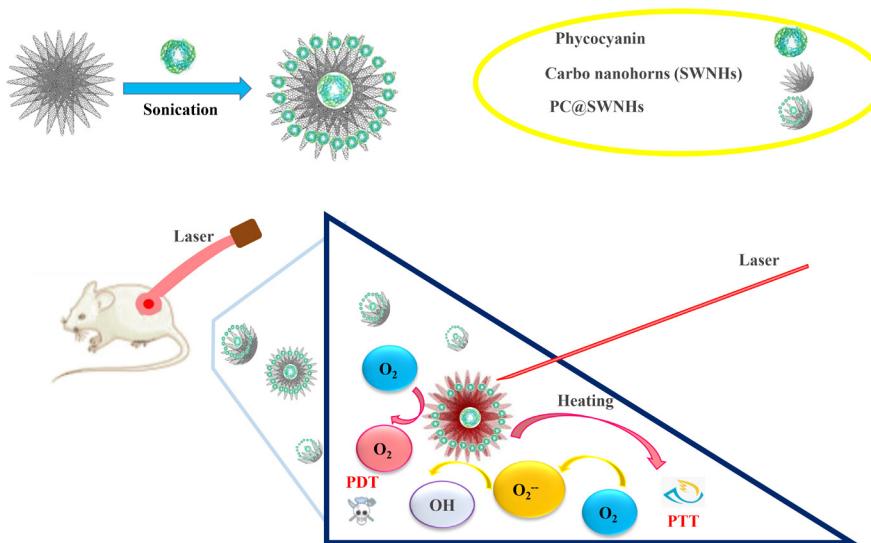


Fig. 6. Schematic diagram of the synthesis method of Phycocyanin @ Single-Walled Carbon Nanohorns.

strated an enhanced anticancer ability in inducing drug to cancer cells than the free CDDP samples. According to the authors, the attachment of the SWCNHs to the cells is responsible for the enhanced quantity of locally release related to CDDP-loaded SWCNHs drugs [107]. Figure 6 depicts a schematic diagram of the synthesis method of Phycocyanin @ SWCNHs and its application for near-infrared light-mediated photodynamic/photothermal cancer therapy [108].

2.7. Soporous Carbons

Nowadays, mesoporous carbon nanoparticles (MCNs), known as an intensifying star in material knowledge, prompt vast study activities, having superior chemical and physical features [109, 110]. MCNs are widely applied as supercapacitors, fuel cells, electrode materials for batteries, matrixes for highly critical catalytic procedures, and sorbents for gas storage and separation procedures [111]. Because of advantages associated with MCNs, including large pore volume, high specific surface area, well-defined surface properties, and tunable pore morphologies, these materials are predominantly more favorable for biomedical applications. The latest research discloses that MCNs can also be applied as nanomaterials with NIR-resonant capability combined with chemo-photothermal therapy drug-loading [112]. Having such interesting properties, they are also used to construct a thermo-chemotherapy platform that can be answered to overwhelm the trials concerning releasing the carried drug and heterogeneous intracellular stimuli [113]. Newly, mesoporous nanoparticles, particularly silica nanoparticles (MSNs), are more attracted to DDSs as drug carriers because of their fascinating features such as low cytotoxicity, high surface area, large pore volume, biodegradability, and easy functionalization. MSN with a diameter < 200 nm, received great attention and could be successfully entreated to cells through intracellular endocytosis. Therefore, these materials are effectively studied with numerous groups as gene delivery vehicles, anticancer drugs, and protein. Despite mesoporous silica, the large quantity of drug charging is facilitated by ordered mesoporous carbons (OMCs) with higher pore volumes and surface areas. Moreover, it is found that carbon nanoparticle cytotoxicity is inferior to silica nanoparticles [110].

In addition, these materials with average particles (150 nm) can be proficiently endocytosed in cervical cancer cells of humans (HeLa). Besides, the reported information showed that MCN materials could act as a transmembrane delivery motor for releasing Fura-2 and a cell tissue resistant fluorescence dye in HeLa [114].

2.8. Carbon Dots

A novel kind of carbon nanomaterial, carbon quantum dots (CQDs), is appealed to significant interest due to their distinctive features, including low toxicity, better cell penetrability, facile production and modifying, exceptional biocompatibility, excellent water solubility, and higher optical characterizations. Therefore, these carbon nanomaterials have shown different favorable applications in sensing, optoelectronics, bioimaging, and theranostic fields [115-117].

Since a few years back, various CQDs have been synthesized using different approaches, for instance, electrochemical, thermal, microwave, and hydrothermal methods. Among these, the hydrothermal processes have broadly been investigated because of the green nature of hydrothermal precursor chemistry. Furthermore, having reasonable biocompatibility and worthy surface functions, CQDs can load platforms in numerous molecules. Especially, functionalized carbon dots with various chemical groups lead them to be engineered to different functionalized molecules, including protein, aptamer, and drug molecules, through noncovalent and/or covalent interaction useful to multipurpose biomedical applications [118]. For instance, Huang et al. (2012) [119] deliberated a new theranostic platform with photosensitizer-conjugated CQDs. The synthesized CQDs-Ce6, upon irradiation, exhibited greater photodynamic efficiency and more robust fluorescence emission than Ce6.

A kind of CQDs, known as Zero-dimensional graphene quantum dots (GQDs), consists of a few layers of graphene sheets with a thickness of < 10 nm in size. These materials are effectively made up by top-down methodologies such as electrochemical and chemical exfoliation, microwave/ultrasound-assisted exfoliation, and hydrothermal/solvothermal exfoliation, or via bottom-up methods, for example, chemical vapor deposition, stepwise cage opening/organic synthesis, and pyrolysis/carbonization [120-122]. They are employed in several bioimaging applications such as the magnetic resonance imaging (MRI), dual-modal and fluorescence, and two-photon fluorescence imaging [123, 124]. They can also be properly applied in electrochemical luminescence, photoluminescence, or the main neurotransmitter sensing (such as norepinephrine, tyrosine, dopamine, acetylcholine, serotonin, and epinephrine), and/or electrochemical sensors [125, 126]. In addition, due to the capability of GQDs for crossing the blood-brain barrier (BBB), these materials can be demonstrated as excellent drug delivery organizations over the bloodstream, up to the brain, and across the BBB. They are also successfully used in therapeutics and neuroscience diagnostics,

Table 1.

A variety of studies on different carbon allotropes in cancer therapy

Carbon allotropes	Study types (in vitro/in vivo)	Drug	Experimental model	Ref.
Nanodiamond	In-vitro & in-vivo	Fluorescein isothiocyanate	C6-Luc glioblastoma cells, U251MG-Luc human glioma bearing NIH nu/nu nude rats	[141]
Nanodiamond	In-vitro	Polyethylene glycol, transferrin	Human hepatoma (HepG2) cancer cell line	[142]
Graphene oxide	In-vitro and in-vivo	Polyethylene-glycol, 1,4,7- triazacyclononane-1,4,7- triacetin acid, NOTA, 64Cu, and follicle-stimulating hormone receptor	Murine lung metastasis model of breast cancer	[143]
Graphene oxide	In-vitro and in-vivo	Polyethylene-glycol, folic acid	B16F0 melanoma tumors using a mouse model	[144]
Graphene oxide	In-vitro	Cyclic RGD chitosan, fluorescein isothiocyanate	Bel-7402, SMMC-7721, HepG2 cell line hepatocellular carcinoma	[145]
Graphene quantum dots	In-vitro	Carboxylic group	MCF 10A, SKBR3, MCF 7, MDA-MB-436, MDA-MB-468, MDA-MB-231, MDA-MB-157, MDA-MB-175VI, HCC1806, and Hs578T cells cancerous, and metastatic human breast cells	[146]
Graphene quantum dots	In-vitro	Folic acid	HeLa cell human cervical carcinoma cells, A549 adenocarcinomas human alveolar basal epithelial cells, and HEK293A normal human embryonic kidney cells	[147]
SWCNTs	In-vitro and in-vivo	Chitosan oligomer, folic acid	A549 cells lines, lung cancer cells, tumor-bearing mouse model [assisted through NIR pulsed laser irradiation (1064 nm)]	[34]
SWCNTs	In-vitro	Polyethylene glycol, folic acid	Breast cancer cell lines (MCF7) & mouse fibroblast cell lines (L929) (assisted through NIR laser irradiation (800 nm))	[148]
SWCNTs	In-vitro	Polyethylene glycol, sgc8 aptamers	Human leukemic lymphoblast cells (CCRF-CEM cells) [Assisted through NIR laser irradiation (808 nm)]	[149]
SWCNTs	In-vitro and in-vivo	Lipid molecule docosanol, folic acid	Human breast cancer, xenograft mouse model (MCF-7 breast cancer cells)	[150]
MWCNTs	In-vitro and in-vivo	Galactosylated chitosan	Hepatic tumor, HepG2 cells & mice bearing hepatocellular carcinoma H22 cells	[151]
MWCNTs	In-vitro and in-vivo	Polyethylene glycol, folic acid	HeLa cell line (human, cervix, epithelial-like, carcinoma)	[152]
MWCNTs	In-vitro and in-vivo	Polyethylene glycol, angiopep-2	Brain capillary endothelial cells (BCEC) & C6 glioma cells (xenograft mouse model)	[153]
MWCNTs	In-vitro and in-vivo	D-Alpha-tocopheryl, polyethylene glycol 1000 succinate (TPGS), transferrin	Human lung cancer cells (A549 cells)	[154]
Fullerene	In-vitro and in-vivo	Diadduct malonic acid, micelles	HeLa cells, S180 tumor-bearing mouse models	[155]
Fullerene	In-vitro and in-vivo	Distearoyl-sn-glycero-3- phosphoethanolamine, polyethylene glycol, Asn-Gly-Arg (NGR)	4T1 cells (mouse breast cancer cell line)	[156]
Fullerene	In-vitro and in-vivo	Poly(lactic acid), L-phenylalanin	Melanoma tumor- bearing mouse models	[157]

for example, photodynamic therapy and photothermal, in combination with chemotherapy or alone [127-129]. Some examples of GQDs-based drug delivery-release modes are enriched retention and permeability, the delivery-release of ligand-pH, (EPR)-pH, and EPR-photothermal delivery-release. Besides, Levy et al. [130], Zhao et al. [131], and Jha et al. [132] reviewed the modes of magnetic thermal/core/shell-photothermal delivery-release.

2.8.1. Unmodified GQDs

The non-cytotoxic dose of GQDs (15 μ g/mL) significantly changed the expression stairs of genes included in the metastasis and growth (PTEN, Bcl2, Box, miR-21, and miR-29a) of cells, breast cancer, and the activity of mitochondrial in the cellular stair, which suggests that the susceptibility and varied cell fate can have abnormality consequence in the GQDs application anticipated results. However, GQDs (50 nm) did not affect a significant diminution in the feasibility of KMBC/71, HUVEC, and MCF-7 cells [133].

In vivo investigations on type 2 diabetic mice displayed that the

complications of GQD and vanadyl compounds presented a late glucose-lowering outline, and a three-week experiment showed a higher significant effect on β -cell protection and insulin development than only vanadyl component. Furthermore, these complexes, probably via the π - π stacking mechanism of GQD sheets, exhibited more *in vitro* membrane penetrability than GQDs and low toxicity related to GQDs [134].

2.8.2. Functionalized GQDs

It was found that Hydroxylated GQDs (OH-GQDs) could decrease the living colonic organoid size and normalize phosphorylated p53 at a three-dimension organoid culture produced via selected crypts [135]. It was also discovered that FA-PEG-GQD-COOH, as a smart drug motor, showed 97.5 % encapsulation efficacy (EE) along with 40.1% drug-loading measurements in mitoxantrone and entered cervical cancer cells of humans mainly through the macropinocytosis-related method. Besides, lower systemic toxicity and robust antitumor proficiency were shown by this nanomaterial [136].

The GQDs with a proper size infused in the biomembrane could

contribute to the drug delivery procedure via decreasing translocation free energy [137]. Water-soluble GQDs bearing DOX are prepared using exfoliation and acidic oxidation of MWCNTs, linked covalently to the module of biotin tumor targeting (BTN). Although both the QGD-BTNs and GQDs are identically low-toxic in concern to A549 cells, GQD-BTN-loaded DOX showed delayed and greater cell uptake than those of GQD-BTN and the free drug. The delayed nuclear internalization of the drug associated with removing the drug from the nano DDS was induced by the acidic environment of cancer cells [138]. Enzalutamide-functionalized GQDs when cross-linked with targeting tumor polyethylene glycol (PEG) and peptides exhibited high drug-loading efficiency by electron π - π interactions. Castration-resistant prostate cancer cells were quickly suppressed by modified GQDs through endocytosis. Moreover, enzalutamide-loaded materials exhibited excellent cancer-targeting and reserved *in vitro* progression lines of LNCaP and C4-2B cells of prostate cancer. Additionally, nanocarriers of GQDs revealed an enriched ability of cancer-targeting, a measured drug release, and improved drug side impacts, proposing that it could be applied in the therapy of an intravenous related to this prostate tumor cell type[139]. A variety of different carbon allotropes applied in cancer therapy are provided in Table 1.

3. Conclusions and future insights

During the last few decades, immense attention is to developing cancer theragnostic agents. Many types of nanostructured materials have been investigated and advanced to theragnostic tumor applications. Among all nanostructured materials, carbon-based materials including graphene, carbon nanotubes (CNTs), nanodiamonds, and fullerenes showed good advantages. In addition, due to their distinctive physicochemical features, they are extensively investigated for the theragnostic of cancer with the vast effective engineering possibility of multi-agent therapeutics and diagnostic functions. Carbon-based nanostructures demonstrate various excellent properties such as unique properties including small sizes, large specific surface areas, sp^2/sp^3 hybridized carbon atoms, tunable pore structures, rigid structures, post-chemical modifying, high thermal and electrical conductivity, wear and thermal resistance, chemical stability, and low friction coefficient. In addition, they could be modified using numerous bio-molecules through different surface coating approaches, possibility via covalent and non-covalent bonding, resulting in surface-functionalized carbon-based nanostructures with improving the regulation and biocompatibility properties within biological systems suitable for theranostic purposes. To provide a comprehensive overview of various types of carbon-based nanostructures and their application in cancer treatment, the current review is focused on introducing the substructures of carbon nanostructured materials, mentioning their physicochemical characterizations, and covering the biomedical applications associated with each carbon allotrope materials, highlighting their uses in targeted drug delivery for cancer therapy.

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Conflict of interest

The authors declare that there is no conflict of interest.

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