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A Review on Biomedical Applications of Carbon Nanomaterials

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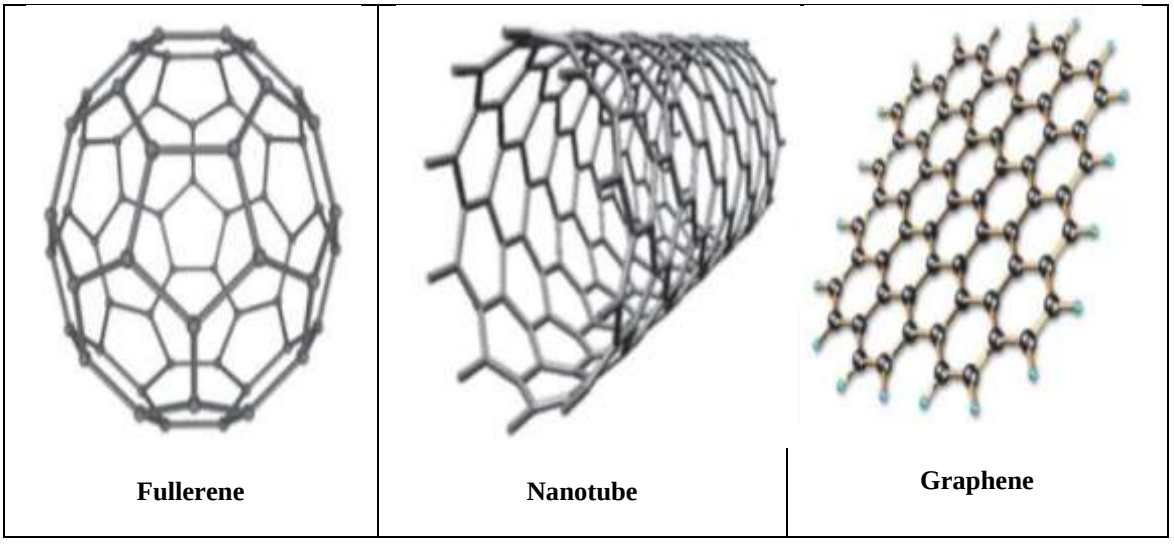
ABSTRACT

With new pathogens such as the Corona virus disease of 2019 and the prevalence of cancer as one of the leading causes of death worldwide, the development of suitable materials to address these challenges has become an important research focus in its field. Researchers around the world are studying new types of materials and biological systems to combat various diseases that affect humans and animals. Carbon nanostructures, with their properties of facile functionalization, drug-loading capacity, biocompatibility, and antiviral properties, have become a primary focus of biomedical researchers. However, reducing toxicity, improving biocompatibility, improving dispersibility, and improving water solubility have been challenges for carbon-based biomedical systems. This article aims to discuss the latest advances in using carbon nanostructures such as fullerenes, graphene, and carbon nanotubes for drug delivery, cancer therapy, and antiviral applications.

Keywords: carbon nanomaterials, cancer therapy, antiviral , antineoplastic activity

I. INTRODUCTION

Selecting suitable materials for drug delivery, cancer therapy, and antiviral applications has challenged biomedical researchers. Carbon nanomaterials possess attractive properties for many biomedical applications because of their structural diversity, large surface area to volume, ease of functionalization, unusual optical properties, and biocompatibility. [1] The variety of nanoscale carbon structures is impressive. At nanoscale dimensions, carbon nanotubes (CNT), graphene, fullerenes, carbon dots (CD), graphene quantum dots (GQDs), carbon fibres (CF), Nanodiamonds, carbon nano onions, and amorphous carbon nanostructures represent alternative structures and allotropes of only one element, carbon. [2,3] The classification of carbon nanomaterials is usually determined by the number of dimensions above the nanoscale (100 nm). [4] Therefore, CDs, GQDs, and fullerenes are zero-dimensional nanomaterials. CNTs and CFs are classified as one-dimensional nanomaterials; layered structures such as graphene are classified as two-dimensional nanomaterials. Finally, nanodiamonds are classified as three-dimensional carbon nanostructures..



Fullerene **Nanotube** **Graphene**

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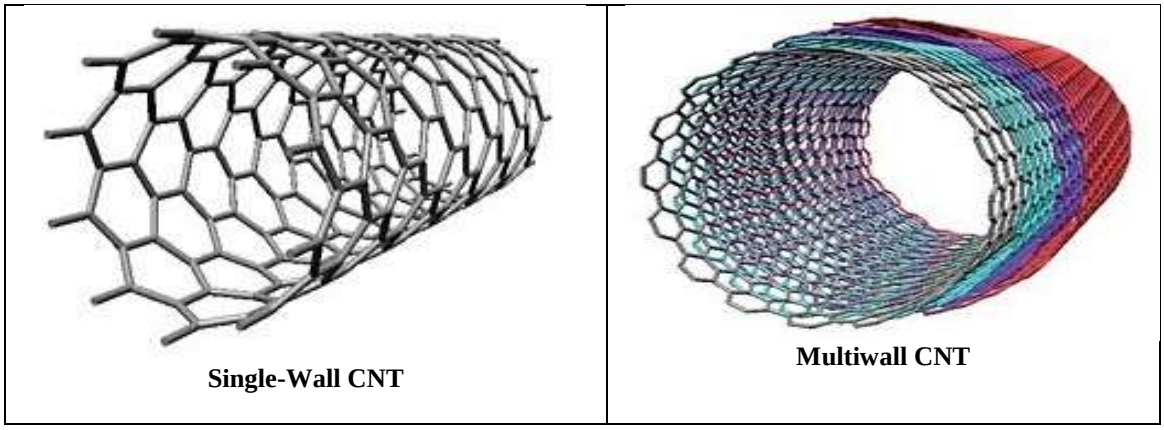

Figure 1-The schematic of main carbon nanostructures

Fullerenes were first discovered in 1985. The inventor of this new carbon allotrope was awarded the 1996 Nobel Prize in Chemistry.[5] This result is considered revolutionary in synthesising carbon allotropes. [2]. Fullerenes are sp2 carbon atom cages of various sizes with single or double bonds (Fig. 1). [6]. Fullerenes enjoy the highest symmetry among the different carbon nanostructures, hence their high structural and chemical stability. The surface of fulllerenes can be modified with multiple functional groups for targeted delivery in drug delivery, diagnostic imaging, and bio-sensing applications. [1,6]. The photoelectrochemical properties of fullerenes, mainly C_{60}, make them suitable for photodynamic therapy.[7] Fullerenes are hydrophobic. The low solubility of fullerenes in polar solvents such as water is an obstacle to their use in biomedical applications. Numerous methods have been used to overcome this obstacle, including synthesising fullerene derivatives. [6, 7]

Graphene is a monolayer of closely packed sp2 carbon atoms. The hexagonal arrangement of this material is shown in Figure 1.[1]Geim and Novoselov reported the synthesis and characterization of this carbon nanostructure in 2004.[8] These efforts earned them the 2010 Nobel Prize in Physics. Compared to bulk structures, this nanostructure has a large specific surface area. Graphene is chemically functionalized and dispersed in various solvents, including water. It has excellent electrical and thermal conductivity and unique optical properties. [1, 8]. In graphene, all atoms are on the surface, providing attachment points for many biomaterials. With all these properties, graphene is an excellent candidate for biosensing, drug delivery, tissue engineering, genetic engineering, bioimaging, and therapy. [1,8].

CNTs, as fullerene cylinders, are rolled sheets of graphene (Fig. 1). These materials consist of single or multiple layers of graphene called monolayers, such as carbon nanotubes (SWCNT) or multiwalled carbon nanotubes (MWCNT).[1] CNTs were first described by Iijima, who synthesised fullerenes by the arc discharge method in 1991.[9] CNTs are stretchable and flexible and have excellent strength.[10] It has high electrical and thermal conductivity and remarkable chemical reactivity. Several barriers prevent large-scale deployment of CNTs. Lack of technology to synthesise CNTs with repeatable structures for mass production .[10]The use of carbon nanostructures to treat emerging viruses such as coronavirus disease 2019 (COVID-19) and established viruses such as Ebola and cancer has been the focus of recent research activity. Several studies have recently been published on using carbon nanostructures for COVID-19 treatment. Many researchers have attempted to bring carbon-based materials closer to clinical drug delivery by functionalizing carbon nanostructures and coupling them with biomolecules. This article highlights recent research on graphene, fullerenes, and CNTs for advanced drug delivery, cancer therapy, and antiviral applications.

Drug delivery and cancer therapy

A compound's biodistribution, pharmacokinetics, and excretion properties play an essential role in the efficacy of a drug delivery system. [11]. Carbon nanostructures are attractive candidates for drug delivery systems because their dimensions are close to those of viruses and other biological structures. Carbon nanostructures can be present in poorly drained physical structures (such as tumours), but not in healthy cells with normal

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drainage. [12]. Carbon nanostructures are easily functionalized and can be conjugated with chemotherapeutic agents, antibodies, antitumor agents, and other therapeutic agents. [3,12].

Fullerenes

Numerous derivatives of fullerenes with improved water solubility have been developed for advanced drug delivery systems. The fullerene and its size and amphiphilicity allow them to penetrate almost all biological entities and barriers. Conjugated fullerenes can be used for local drug delivery and avoid damage to other body organs. For example, ibuprofen is a commonly prescribed drug to reduce pain and inflammation and, when taken orally, has side effects such as gastrointestinal bleeding, ulcers, indigestion, and vomiting. Recent density functional theory (DFT) calculations have shown that C_{60} fullerenes containing porphyrin-like transition metal N4 can be used as ibuprofen carriers. Quantum studies confirmed drug release in acidic environments in unhealthy cells.[13]

The use of fullerenes in nucleic acid delivery systems has recently attracted attention. A recent in vitro study used tetra (piperazino) [60] fullerene epoxide (TPFE) to stabilise and transport labile siRNA molecules.[14] In vivo studies have shown that TPFE has no toxicity and high knockdown efficiency for siRNA delivery, in contrast to the commonly used Lipofectamine 2000.[15] As shown in Figure 2, in vitro studies used submicron-sized His TPFE siRNA particles to deliver siRNA to lung cells. There was immediate aggregation with plasma proteins. TPFE-siRNA plasma protein material was initially stable and accumulated in pulmonary capillaries, and it then destabilised after blocking pulmonary veins and releasing siRNA into cells. TPFE residues in the form of micelles were less than 10 nm and cleared from pulmonary capillaries with a high clearance rate. [14]

The blood-brain barrier (BBB) contains tight junctions that act as a barrier to delivering highly polar drugs to the central nervous system (CNS). Fullerene-based carriers have been shown to allow penetration into the BBB. For example, the effect of fullerene compounds on BBB penetration by polar hexamethonium benzene sulfonate was studied. This study prepared a "substantially solvent-free planar lipid bilayer" phosphocholine membrane [16]. In the absence of fullerenes, adding hexamethonium benzenesulfonate to lipid bilayers did not produce observable trans-membrane currents. However, fullerene compounds (IEM-2143 and IEM-2144) enhanced ion permeability across phosphocholine bilayers, lipid disruption at phosphorus line membranes, and movement across lipid bilayers.[16]

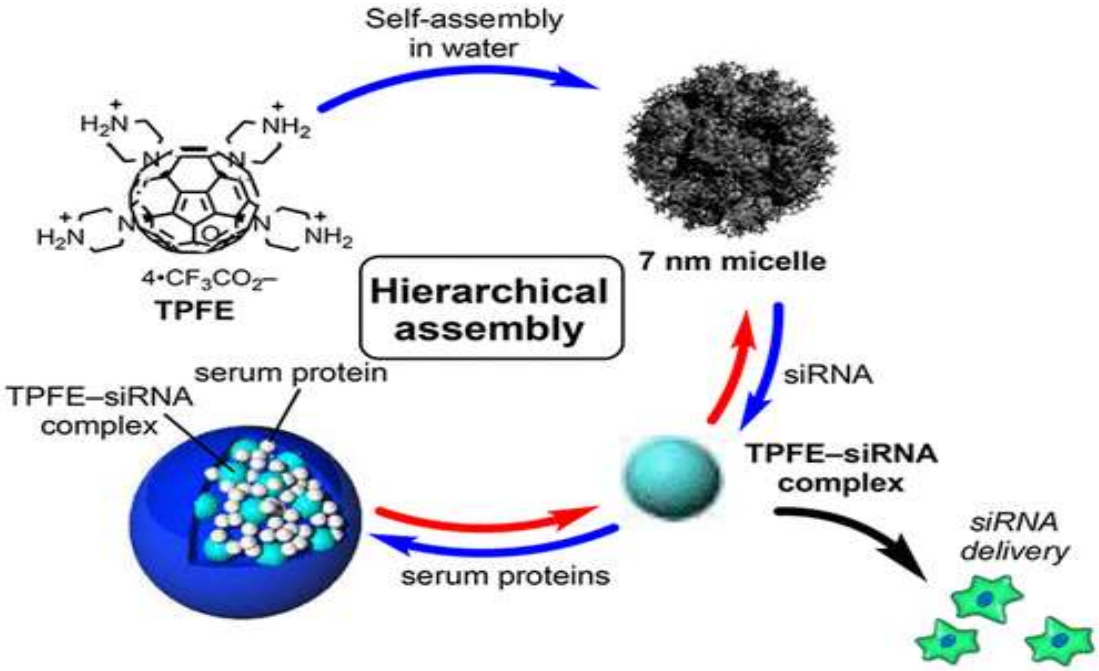

Figure 2-Schematic of producing TPFE-siRNA-plasma protein for siRNA delivery

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This is shown by research on the COVID-19 pandemic. Chloroquine (CQ) may be an effective drug to combat the COVID-19 infection.[17]Due to the excellent energetic match between these species, DFT studies indicate that Al- and Si-doped C_{60} is a stable CQ carrier for COVID-19 therapy. Fullerenes act as electron acceptors, and CQs act as electron donors.[17]Chemotherapeutic procedures for lung cancer have insufficient concentrations of drugs that interact with tumour cells and are plagued by drug toxicity. As an alternative to conventional lung cancer chemotherapy, various water-soluble fullerene derivatives for drug delivery have been investigated for their anticancer potential. The more potent cytotoxicity of fullerene derivatives to lung cancer cells corresponds to the low presence of aliphatic single bonds on the fullerene cage, the absence of chlorine in the structure, and the presence of 2-phenoxyacetic acid residues. [18].

A highly effective drug for pancreatic cancer is gemcitabine. However, this agent shows some chemo resistance and poor distribution within tumours. Therefore, alternative mechanisms of gemcitabine delivery are an important focus of current research efforts. A possible solution is to combine gemcitabine with [60] fullerene to improve water solubility.[12]

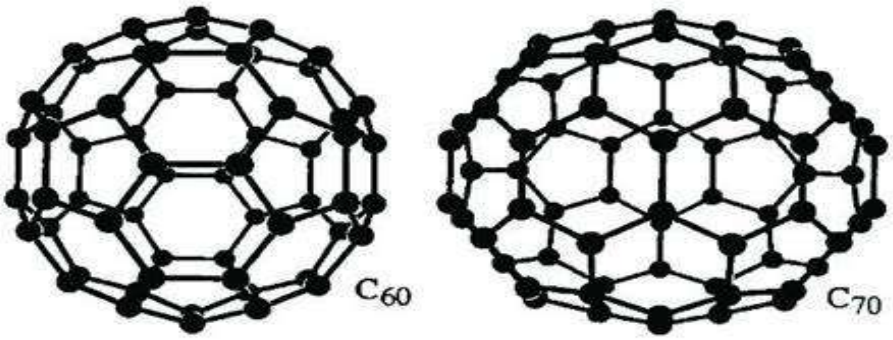

Figure 3- Fullerenes C60 and C70

This compound exhibits enhanced cytotoxicity by oxygen species generated by C_{60} upon illumination with a blue LED [12]. C_{60} conjugated with serinolamide penetrates hepatoma cells. C_{60}-serinol conjugated to paclitaxel reduces tumour size without the side effect of weight loss. Studies on the in vivo function of C_{60}-serinol have shown rapid and efficient bio-distribution and renal clearance in mice.[19] The calculated results show that the C_{60} can be loaded successfully with the chemotherapeutic drug doxorubicin (DOX) and the antineoplastic boronchalcone [20].

A new drug delivery system was developed by Shi et al. for advanced cancer treatment with C_{60}[21]. Unlike traditional drug delivery systems, this "off-on" type of drug delivery system does not have the problem of uncontrolled drug release. In this approach, fullerenes are combined with DOX using reactive oxygen species (ROS) to form a hydrophilic shell that adheres to its surface with tumour tropism. In "off" mode, DOX is stably trapped in a pH 5.5 environment. However, when switched on, fullerenes cause him to generate ROS, resulting in the release of DOX. The switch between the on and off modes is remotely controlled by a 532nm laser.[21]

Some C_{60} derivatives can generate ROS upon exposure to light. Examples include sugar-linked C_{60} derivatives that target cancer cells[23]. Cancer cells tend to accumulate glucose and attract the glycoconjugate C_{60}. Based on recent research, these glycol fullerenes are taken up by cancer cells. When exposed to blue and green light, it acts as a photodynamic cytotoxic agent.[22]

Graphene

Although graphene has the potential to be used as a drug carrier, it has toxic effects on human organs because it can agglomerate in tissues and generate oxidative stress. To fix this problem, the surface modification of graphene is considerable. Different functional groups can be attached to the graphene surface through the deep eutectic solvent (DES) method to overcome these problems. The functionalization of graphene allows for broader applications in advanced drug delivery applications. In addition, graphene's large surface-to-volume ratio is beneficial for drug delivery applications. Zainal-Abidin et al. describe the DES

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functionalization of graphene with choline chloride and loading with DOX. This material shows good dispersibility and good DOX loading capacity. It exhibits superior antitumor activity because DOX is captured by functional graphene more efficiently than pristine graphene [23, 24].

Graphene materials have recently been developed for pH-sensitive drug delivery. Unlike normal cells, cancer cells have an acidic environment. As such, pH-sensitive materials can be helpful in drug delivery systems. For example, a rubber nanohybrid hydrogel containing pure graphene has been developed for pH-sensitive drug delivery applications.[25]This material exhibits drug release with changes in pH. Furthermore, the conductive nature of the hydrogel allows for rhythmic and tunable drug delivery. The pH oscillation response of the hydrogel has been demonstrated by measuring the rise and fall behaviour of the hydrogel in a buffer solution such as pH buffer. The solution has been adjusted between 7.8 and 1.7. This study indicates that the nanohybrid hydrogel is pH-sensitive and conductive due to the contribution of acrylic acid and the graphene components of the structure.[25] In another study, GQD was combined with the reverse transcriptase inhibitors CHI499 and CDF119 for the treatment of human immunodeficiency virus (HIV). GQD has also been shown to permeate the BBB .[27]

Lucherelli et al. attach folic acid to graphene using PEG chains for targeted DOX delivery; they used indocyanine blue to track the compound inside cancer cells to observe its dispersion and antitumor activity. In vitro and in vivo studies have shown reduced toxicity to multifunctional graphene [28]. A new method for fluorinating graphene with an ionic liquid has been investigated to deliver curcumin. The functionalized material showed higher drug loading efficiency and more potent antitumor effects. [29]Combining drugs plays a central role in cancer treatment, as treatments involving a single anticancer drug are not always successful. Due to its simple functionalization and relatively large surface area, graphene is a promising material for combined drug delivery. [30] Computer research shows that graphene can be combined with paclitaxel and DOX. Folic acid-functionalized graphene can co-distribute DOX and camptothecin through strong peptic interactions.[31, 32]
Recent DFT calculations show that FeN4-bound graphene is an excellent adsorbent carrier for ibuprofen; the ibuprofen/FeN4-graphene system is highly chemically bound to the target biological structures [33].

Carbon nanotubes

CNTs are hydrophobic materials that exhibit non-uniform dispersion in the biological environment. Surface functionalization of CNTs can overcome this limitation. When exposed to oxidising agents, CNTs form carboxylated surfaces. Carboxylated CNT materials are drug-loadable, biocompatible, and have uniform dispersions. Carboxylated SWCNTs can be loaded with droxidopa using amine and carboxylate groups. Droxidopa is used as a treatment for orthostatic hypotension and Parkinson's disease. Molecular dynamics simulations predict good stability for this material. [34].

A cell-penetrating MWCNT targeting functionalized cancer has been described. Results with the indicated material show an increase in the level of ROS-supported antitumor activity, high BBB permeability, and efficacy against glioma. BBB infiltration and the compound's selectivity for glioma cells are related to the antitumor function of the material .[35]

Viral neuroleptic disease, caused by a neuroleptic virus (NNV), targets the central nervous system in fish; reaching this affected tissue with drugs is a technical challenge. Fluorescein is thiocyanate (FITC), and isoprinosine, an anti-NNV agent, was combined with SWCNTs to increase isoprinosine delivery efficiency. A delivery system consisting of bovine serum albumin, isoprinosine, and SWCNT has been investigated both in vitro and in zebrafish larvae and showed increased resistance to NNV with significantly reduced mortality. [36].

SWCNTs have also been successfully used to improve the efficacy of immature pearl grouper vaccines against iridovirus. Immune-effect genes were enhanced by using SWCNT as a vaccine carrier.[38]Besides increasing toxicity to healthy tissues, the synthesis of CNTs prevents the direct estimation of the cytotoxicity of the anticancer drug delivery system. To facilitate uniform dispersion and biocompatibility of CNTs, Pennetta et al. functionalized SWCNTs and MWCNTs with covalent (CNT/PPGPc) and non-covalent (CNT/PPGP) pyrrole polypropylene glycol (PPGP) and conjugated these materials with DOX. New CNT/PPGP/DOX systems are associated with melanoma and lung cancer cell death at lower DOX doses. The uniformly

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distributed CNT, PPGP, and DOX also facilitated the assessment of cytotoxicity .[38]

Other novel efficient cancer delivery systems containing CNTs and DOX include PEGylate discrete multiwalled CNTs, MWCNTs for HNO3/H2SO4 oxidation, and ɣ-Fe2O3 nanoparticle coating for magnetic delivery of drugs 40 and polyamholytics. SWCNTs are functionalized by an intercalated polymer (PMT). 41CNTs exhibit the ability to specifically target a specific receptor or molecule. A dual-targeting system has been proposed to increase the effectiveness of anti-breast cancer therapy. Cancer cell glucose transport proteins and folic acid receptors in this system are simultaneously targeted by loading CNTs with DOX and folic acid-conjugated glycoblock copolymers 42. Table 1 summarises recent drug delivery and cancer treatment advances with the aforementioned carbon nanomaterials.

Antiviral applications

With the emergence of new viruses such as COVID-19, the development of new antiviral systems, including drugs and vaccines, has recently attracted considerable attention and interest from the research community. Carbon nanostructures have shown promising antiviral properties such as antiviral activity and blocking of viral enzymes to fight viruses such as HIV, influenza, herpes simplex (HSV), and COVID-19. [43,44]The use of carbon nanomaterials for antiviral applications is currently in its early stages and requires further research.

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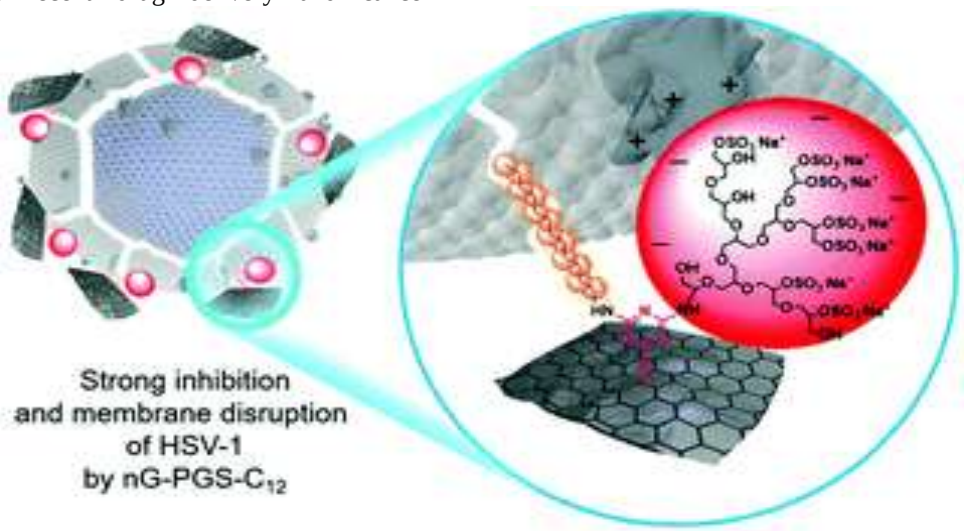

Figure 4- A representation of the inhibitory interaction of C12 with HSV-1

Fullerenes

Hydrophilic fullerenes are of particular interest for antiviral applications. The biological properties of fullerenes directly correspond to the types of functional groups associated with the fullerene's cage. The most water-soluble fullerene derivative is C_{60} [P (O) (OK) 2]5H with a C-P connection to the cage; the synthesis of this material has recently been greatly simplified. [45] In vitro studies of the antiviral effects of C_{60} [P (O) (OK) 2]5H showed potent activity against influenza A and feline coronavirus. [45]Klimova et al. report that water-soluble C_{60} (ndC_{60}) is active against herpes simplex virus type 1 (HSV-1) and human cytomegalovirus. In vitro and in vivo studies have shown that ndC_{60} inhibits virus entry into host cells by blocking interactions with virus receptors. [46]

The coronavirus's outermost layer (envelope protein) is a hydrophobic phospholipid responsible for the interaction with the host. Aqueous colloidal fullerene releases singlet oxygen under UVA irradiation, damaging the lipid layer of the coronavirus. Therefore, the C_{60} coating can serve as an antiviral surface. In addition, it is possible to minimise the adhesion of the virus to the surface. Fullerene-coated surfaces take advantage of the virus's lipid structure and the fullerenes' hydrophobic properties by reducing the viral surface area.[44]A computer study showed that fulleropyrrolidin derivatives could disrupt the primary mechanism by which coronaviruses protect against antibodies, which are deactivated by the

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spike protein receptor binding domain on the coronavirus.[47]

The size of the fullerene derivatives corresponds well to the HIV protease active sites and can block HIV enzymes. The requirement for fullerene derivatives with effective anti-HIV activity is hydrophilicity and a balance between cytotoxicity and antiviral effects. Voronov et al. introduced five novel water-soluble [60] fullerene derivatives as HIV inhibitors [48] by the reaction between C60C16 and dimethyl 2,2'-(1,4-phenylenebis-)(oxygen) diacetate. They found that these five derivatives were active against the R5 and X4 strains of the HIV-1 virus.

Graphene

Besides combining with antiviral materials, graphene can directly interact with viruses. Graphene can interact with viruses through electrostatic and hydrophobic interactions to affect the viral envelope. [49]A newly discovered direct interaction mechanism was reported by Matharu et al. [50]. They investigated the antiviral activity of graphene nanoplatelets (110 nm × 170 nm) by incubating the suspension for 24 hours with graphene in the phage Escherichia coli T4, a double-stranded DNA virus. Graphene nanoplatelets significantly reduce the number of virions and completely suppress infection for 3 hours. They attributed the antiviral effect of graphene to its morphology and the generation of ROS [50]. Another recent study showed that a graphene and copper-containing hybrid material inhibited the attachment and entry of influenza virus into host cells within 30 min by destroying the virus envelope. [51]

Graphene can be combined with negatively charged antiviral drugs (e.g., negatively charged sulfates). [52]This conjugation enhances the interaction between graphene and the positively charged residue of the virion.[53] Donsky et al. [53] functionalized graphene to enhance its antiviral activity. They synthesised graphene derivatives conjugated with polyglycerol sulphate and alkyl chains (C3eC18). Graphene with a C12 alkyl chain acted as the best HSV-1 inhibitor (Figure 4); however, it shows strong toxicity to Vero cells. Shorter chains of C12 are not cytotoxic to Vero cells but serve as good HSV-1 inhibitors.

There are several suggestions regarding using graphene as a COVID-19 inhibitor based on computer simulations and experimental results of other RNA viruses of the coronavirus family. [54, 55] They suggest that graphene can destabilise the COVID-19 virus. Graphene's strong light-absorbing properties can act as a disinfectant. [54, 55].

Carbon nanotubes

The RNA-binding domain (RBD) of nonstructural protein 1 (NS1) in influenza A facilitates virus survival and prevents mRNA export from host cells. Molecular dynamics simulations have predicted that CNTs can rapidly adsorb and elongate RBD and disrupt the viral defence system. [56]The effect of nonfunctional SWCNTs and hydroxylated MWCNTs on the H1N1 A/Mexico/4108/2009 (IAV) strain in lung tissue was evaluated by Chen et al. They note that physical exposure to MWCNTs and IAV alters the antiviral response to the virus without changing viral titers or causing significant lung damage; SWCNTs produced higher viral titers with lung injury under the same conditions in vivo. [57] MWCNTs show phagocytosis by macrophages; the shedding characteristics of MWCNTs are significantly faster than those of SWCNTs. [57]The use of SWCNTs as an antiviral coating on the surface has been suggested based on the results of DFT studies.[58]According to the DFT results, the SWCNTs with Ru-, Pt-, and Cu functions strongly adsorb H2O2 molecules, causing the death of viruses such as coronavirus.

Table -1 recent progress in drug delivery and cancer therapy using carbon nanomaterials

Carbon nanomaterial	Application	New progress
Fullerene,C_{60} with porphyrin-like transition metal-N4	Drug delivery, ibuprofen	Predicts the release of ibuprofen in an acidic environment of unhealthy cells
Fullerene ,Al-and Si-doped C	Drug delivery, chloroquine	Possible covid -19 treatment by drug delivery
water-soluble fullerene derivatives	Cancer therapy	Water soluble fullerene derivatives with cytotoxicity for lung cancer
[60]Fullerene-glycine derivative	Cancer drug delivery, gemcitabine	New synthetic approach for a highly water-soluble [60]

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C_{60} -serinol	Cancer drug delivery , paclitaxel	Synthesizing a novel C_{60} derivative
C_{60}	Cancer drug delivery,Doxorubin and Boronic Chalcone	The possibility of functionalizing C_{60} with B and N atoms and loading with doxorubicin and boronic chalone
Glycoconjugate C_{60} Derivatives	Cancer therapy	Glycolfullerenes act as photodynamic cytotoxic agents.
Functionalized graphene with choline chloride	Cancer drug delivery, doxorubicin	First doxorubicin delivery by graphene
Graphene with attached folic acid and indocyanine green	Cancer drug delivery, doxorubicin	Multifunctional graphene synthesis with improved anticancer activity
Fluorinated graphene	Cancer drug delivery , curcumin	Synthesis of fluorinated graphene with ionic liquid for the first time and curcumin delivery
Folic acid functionalized graphene	Combined drug delivery, Doxorubicin and Camptothecin	Enhance the efficiency of cancer therapy
Graphene	Combined drug delivery, Doxorubicin and Paclitaxel	Enhance the efficiency of cancer therapy
Graphene with attached FeN4	Drug delivery, Ibuprofen	High chemical bonding potential to target bio-entities
Carboxylated CNTs	Drug delivery, Droxidopa	Uniformly dispersed and biocompatible with excellent system stability
SWWCNTs	drug delivery, Isoprinosine	Enhanced anti-NNV ability
SWCNTs	drug delivery, bath vaccine	Enhanced the efficacy of the bath vaccine
Functionalized SWCNTs and MWCNTs with PPGP	Cancer drug delivery, doxorubicin	Foster the uniform dispersibility and biocompatibility of CNTs and easier cytotoxicity evaluation.
PEGylated multiwalled discrete CNTs	Cancer drug delivery, doxorubicin	The successful anticancer delivery system
Polyampholytic alternating polymers(PMT) functionalized SWCNTs	Cancer drug delivery, doxorubicin	The successful anticancer delivery system
CNTs conjugated with glycoblock copolymers and folic acid	Dual targeting system	Increase the efficacy of anti-breast cancer activity

II. CONCLUSION

This article reviews recent advances in using fullerenes, graphene, and CNTs for drug delivery, cancer therapy, and antiviral activity over the past few years. Because of their nanoscale size, these materials have high surface-to-volume ratios and high chemical reactivity. These nanoscale structures can penetrate various structures and biofilms to facilitate drug delivery.

Future perspectives

Significant progress has been made in the chemical modification of carbon nanostructures and the introduction of new derivatives to improve solubility and biocompatibility, reduce toxicity, stimulate antineoplastic activity, and ensure stable loading of drugs (e.g., antiviral). Although most studies have highlighted the benefits of local drug delivery and the reduction of side effects from the use of carbon nanostructures, the toxicity and safety of these materials need further investigation.

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