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A Review of Carbon Nanomaterials Research Applications in Biomedicine

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Abstract: *Carbon nanomaterials have emerged as a significant research area in biomedicine. The rapid development of nanotechnology and the growing need for advanced biomedical solutions have led to extensive investigations into carbon nanomaterials. This review aims to comprehensively analyze their research and application status in biomedicine both domestically and internationally, covering aspects such as their unique properties, roles in disease diagnosis, treatment, and rehabilitation. By doing so, it not only anticipates potential technological advancements but also addresses the increasing demands in the biomedical field. The significance lies in providing valuable insights and a reference for peers, guiding further research and application directions, and ensuring that carbon nanomaterials continue to play a crucial role in enhancing biomedical technologies and improving patient care.*

Keywords: *Carbon Nanomaterials, Biomedicine, Cancer Therapy*

1. Introduction

Carbon nanomaterials have emerged as a highly significant and rapidly evolving area of research within the realm of biomedicine. Since the 1990s[1], their development has been nothing short of remarkable, with far-reaching implications for the diagnosis, treatment, and rehabilitation of various diseases. In the domain of disease diagnosis, the early 2000s marked the inception of investigations into the utilization of carbon nanotubes and graphene for biosensing applications. These initial efforts laid a solid foundation for the subsequent emergence of highly sensitive and specific detection methods. Through continuous research and innovation, these carbon nanomaterials have been engineered to interact with biomolecules in a precise and selective manner, enabling the accurate identification of a wide array of biomarkers and the early detection of diseases. In the area of disease treatment, around the mid-2000s[2], the remarkable potential of carbon nanomaterials for drug delivery and cancer therapy was recognized. Studies began to focus on their unique ability to act as carriers for chemotherapy drugs, leveraging their physicochemical properties to enhance drug solubility, stability, and targeted delivery. Additionally, their integration into photothermal and photodynamic therapies opened up new avenues for combating cancer, with the ability to precisely target and destroy cancer cells while minimizing damage to healthy tissues. In the rehabilitation field, it was during the 2010s that the application of carbon nanomaterials in tissue engineering, particularly in cardiac and neural tissue engineering, started to gain substantial momentum. Their exceptional mechanical, electrical, and chemical properties have provided novel opportunities for tissue regeneration and repair. By mimicking the natural extracellular matrix and promoting cell adhesion, proliferation, and differentiation, carbon nanomaterials have shown great promise in restoring damaged tissues and improving functional outcomes. As of 2024, carbon nanomaterials continue to exhibit immense potential in biomedicine. Their distinct physicochemical characteristics, such as high surface area, tunable porosity, and excellent biocompatibility, enable a wide range of applications, from targeted drug delivery systems that precisely release therapeutic agents at the site of disease to tissue regeneration scaffolds that support the growth and integration of new tissues. However, several challenges still loom large, including issues related to solubility, bioavailability, and long-term stability in vivo. Despite these hurdles, the field is advancing at a rapid pace, with ongoing research efforts aimed at optimizing the properties and performance of carbon nanomaterials. This review undertakes a comprehensive analysis of the research and application status of carbon nanomaterials in biomedicine, spanning their diverse roles in disease diagnosis, treatment, and rehabilitation. By synthesizing the current knowledge and highlighting the latest advancements, it provides invaluable insights and guidance for future research and application directions, serving as a crucial resource for scientists, clinicians, and researchers in the field.

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2. Carbon nanomaterials

2.1 Preparation of carbon nanomaterials

Carbon nanomaterials are prepared by various methods. Chemical vapour deposition is one of the commonly used ones, in which carbon nanomaterials are formed by high temperature decomposition of a gaseous carbon source under the action of a catalyst, and carbon atoms are deposited on a substrate, which can be precisely controlled in terms of its growth direction and size [3]. The arc discharge method involves the formation of carbon nanotubes, among others, by the evaporation and recrystallisation of graphite through an arc discharge between two graphite electrodes in an inert gas environment [4]. There is also the laser ablation method, which uses high energy.

A quantum density laser beam irradiates a carbon target, and the resulting carbon plasma forms carbon nanomaterials during the cooling process. The solution method is less costly, and nanomaterials such as carbon quantum dots are prepared in solution systems using organic synthesis reactions [5]; these methods have laid the foundation for the research and application of carbon nanomaterials.

2.2 Physicochemical properties of carbon nanomaterials

Carbon nanomaterials are not easily soluble in water and can maintain good properties in circulation; they have a special structure, which can be combined with functional groups and special antigens to have the effect of targeted drug transport, which are mainly combined through covalent forms (e.g., liposomes[6]) and non-covalent forms (e.g. polyethylene glycol[7])[8]. The physicochemical properties of carbon nanomaterials change when they are combined with functional groups, such as the water solubility and biocompatibility increase when they are combined with polyethylene glycol[9-10]; if the drug is mounted on carbon nanomaterials, the carbon nanomaterials can control the drug release according to the change of the environment, for example, the change of the surrounding pH[11] , temperature, etc., which will affect the speed of the drug release and the amount of drug release, and it can keep sufficiently constant concentration of the chemotherapeutic drug in the tumour, and prevent the chemotherapy drug from being released in a constant concentration. It can keep the chemotherapeutic drug at a constant enough concentration in the tumour and prevent the chemotherapeutic drug from being released in normal tissues. The modifiability of carbon nanomaterials and their ability to control the release of drugs have broad application prospects in the biomedical field. Materials such as genes and proteins have also been loaded onto carbon nanomaterials for research.

3. Carbon nanomaterials in biomedical applications

3.1 Carbon Nanomaterials in Disease Diagnostics

Currently, the sensing platforms designed based on carbon nanomaterials are mainly applied to the detection of biomolecules in samples such as human serum, sleeping fluids, or commercial pharmaceuticals, e.g., Yi et al [12] designed and synthesized a carbon dotted nanoenzyme hydrogel, which combined with 5,7-dimethoxycoumarin fluorescent probe to construct a colorimetric/fluorescent complementary sensing platform for wide-range, selective, and sensitive detection of oxyphosphorus. Wang [13] et al. synthesized two functionalized copper-based MOFs nanoenzymes by a simple hydrothermal method through functionalized modification of the ligands, investigated their enzyme-like catalytic activities, and constructed sensing platforms for the detection of glucose and acetylcholinesterase, respectively. In addition, the fluorescence properties of quantum dots can be modulated by changing the size, morphology, composition and surface groups. As novel fluorescent nanomaterials, silicon quantum dots (Si QDs) and molybdenum disulfide quantum dots (MoS_2 QDs) have the advantages of high fluorescence intensity, biocompatibility and low toxicity, and thus show great potential for the construction of biosensing platforms. Liu et al. synthesised Si QDs and MoS_2 QDs with different optical properties, and combined these two quantum dots with other molecules or nanomaterials to construct a fluorescence and colourimetric dual-mode sensing platform for the detection of various biomolecules, and the sensing system has been successfully applied [14]. However, a single carbon nanomaterial is no longer sufficient for the quantitative detection of trace amounts of substances, but researchers and scholars do not have a thorough understanding of how the synergistic effect between multiple carbon nanomaterials, whether there is a chemical interaction with the target molecules that enhances or attenuates the electrochemical signals, and there is insufficient knowledge of the effects of the structure of the composite materials, so the research on the modification of electrochemical sensors with carbon nanomaterials still needs to be further deepened. Liu[15] et al. designed an epinephrine electrochemical sensor based on carbon nanomaterials. It was found that carbon nanomaterials could not only increase the specific surface area and active sites of the materials to improve the performance of the electrochemical sensors, but also have interactions (e.g., π-π interactions) with the adrenaline molecule, which made the constructed electrochemical sensing interfaces able to detect adrenaline in a more stable, rapid and sensitive manner. Carbon nanomaterials have also breathed new life into the development of flexible and multimodal compatible neuroelectrode technologies. Graphene and carbon nanotube-based neuroelectrodes enable simultaneous electrophysiological measurements and optical modulation as well as DBS-fMR coupling, which provide a powerful tool for the study of neural circuits in the brain and the study of DBS therapy for neurological diseases [16]. In future studies, its practical application in cells or organisms needs to be further probed. In addition, the developed assay needs to be applied to more clinical samples and the results of the assay need to be compared with other clinical tests to validate the usefulness of the constructed analysis system for clinical diagnosis.

3.2 Carbon nanomaterials in disease treatment applications

3.2.1 Carbon nanomaterials for drug delivery applications

In the field of cancer therapy, novel nanomaterials present new opportunities for drug delivery and treatment modalities. Nanomaterials can carry drugs or biomolecules (e.g., nucleic acids, peptide chains, etc.) through π-π stacking, hydrogen bonding, electrostatic interactions, hydrophobic interactions, etc. Nanographene oxide (NGO), for example, is a promising new 2D nanomaterial, and a study by Kachousangi et al [17] demonstrated its advantages as a drug carrier. They utilised a pH-sensitive graphene oxide-based nanocomposite to load the drug adriamycin (Doxorubicin) and evaluated its loading and release at different pH values. The results showed that the composite released twice as much at pH=5.5 as at pH=7.5, with a drug loading rate of up to 79%, and this excellent performance effectively improved the release and loading of DOX and provided a more ideal carrier for drug delivery. The low cytotoxicity and low tissue invasiveness of oncological photothermal therapy have led to its widespread clinical application. However, some studies have shown that the non-uniform distribution of thermal energy within the tumour and the limited tissue penetration ability of near-infrared light have resulted in the inability of photothermal therapy to completely eliminate the tumour. Therefore, photothermal therapy is often combined with chemotherapy and immunotherapy for clinical elimination of tumours and prevention of tumour recurrence [18]. As a highly efficient photosensitizer and excellent drug delivery carrier, NGO can combine photothermal therapy with chemotherapy and immunotherapy [19] for clinical tumour treatment. For example, Xu et al. developed a 6-arm polyethylene glycol (PEG) functionalized NGO, which encapsulated the chemotherapeutic drug paclitaxel through π-π stacking and hydrophobicity, which not only improved the solubility of the hydrophobic drug paclitaxel, but also markedly increased the tumor uptake rate of the drug. Compared with single-drug paclitaxel, the NGO-loaded system significantly increased the drug concentration of paclitaxel inside the tumour and its killing effect on tumour cells A549 and MCF-7 was increased by 33.1% and 34.8%, respectively. Pei et al[20] designed a multi-drug nano-delivery system by loading chemotherapeutic drugs cisplatin and adriamycin through 4-armed PEG-modified NGO, where cisplatin, through the reaction of amide Cisplatin was covalently bound to NGO, and adriamycin was adsorbed onto the surface of NGO through hydrophobic interaction. Cellular experiments showed that the multi-drug delivery system could effectively deliver cisplatin and adriamycin to the tumour cells, and the apoptosis and necrosis rate of the tumour cells was increased 2-fold compared with that of single-agent cisplatin or adriamycin; in vivo experiments demonstrated that the multi-drug delivery system of the NGO significantly reduced the toxicity and side-effects of the chemotherapeutic drugs cisplatin and adriamycin on the normal tissues, and significantly increased the in vivo anti-tumour effect of single-agent drugs.

Chemotherapy is one of the important methods in the treatment of advanced nasopharyngeal carcinoma, but there are some urgent problems to be solved. The weak targeting of systemic drug delivery and the poor efficacy of single-agent application make a new type of targeted multidrug-carrying nanomaterials urgently needed. To meet this challenge, Yu et al. constructed a drug delivery system based on graphene quantum dots (GQD or GQD s) targeting the Epidermal Growth Factor Receptor (EGFR). This cisplatin-targeted drug delivery system exhibits good histocompatibility and enables monitoring of intracellular drug release processes by imaging at the level of individual cancer cells. The targeted, multi-drug and pH-dependent drug release characteristics of this system can enhance the efficacy of chemotherapy and reduce systemic side effects in nasopharyngeal carcinoma, and its anti-tumour mechanism may be related to the inhibition of tumour cell proliferation and the induction of cell apoptosis.

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3.2.2 Carbon nanomaterials for cancer therapy applications

Currently, cancer has become one of the major causes of human mortality. Most traditional cancer treatments have adverse effects and short duration of efficacy maintenance [21-22]. In this context, the exploration of novel therapeutic means and materials has become a research hotspot. Carbon nanomaterials show great potential in the field of cancer therapy due to their unique physical properties. It plays an important role in cancer detection and gene therapy. For example, Han et al [23] used doped carbon quantum dots to enhance fluorescence, which enabled sensitive detection of cancer biomarkers. Carbon nanomaterials are even better in cancer therapy. It has good biocompatibility, deep tissue diffusion, and good photothermal conversion ability in the near infrared range, so it is widely used in phototherapy treatment of cancer [24]. Ahmad et al [25] attacked cancer cells by modifying graphene oxide to increase its near-infrared absorption properties and enhance phototherapy intensity and biocompatibility. In addition, carbon nanomaterials undergoing surface chemical modification can provide many benefits. It can improve structural stability and modulate hydrophilicity while enhancing therapeutic efficacy and bioactivity, as well as reducing immune responses. It has been found that acidified carbon nanotubes in combination with phototherapy can be used for the treatment of breast cancer, and significant increases in T cells and macrophages were observed in a study of acid-functionalized carbon nanotubes combined with cryotherapy for the treatment of tumours [26].Aoki et al [27] found that glycosylated chitosan carbon nanotubes carbon stimulated the natural killing of cancer cells by phototherapy, promoted macrophage value-addition and activation, and synergistically achieved immune-mediated tumour metastasis inhibition. Phototherapy and immunotherapy have made breakthroughs in the field of cancer treatment. Carbon nanomaterials have received great attention from researchers as modulators due to their unique thermal conductivity, electrical properties and specific surface area. Zhao et al [28] reported an ultrasmall tin-iron oxide ($SnFe_2O_4$) nanoenzymes regulating the tumour microenvironment. The prepared ultrasmall tin-iron oxide nanoenzymes possessed catalase-like and glutathione peroxidase-like activities. In the tumour microenvironment, activation of H_2O_2 leads to chemodynamic therapy to produce -OH in situ, and depletes glutathione (GSH) to attenuate the tumour's antioxidant capacity. At the same time, the nano-enzyme catalyzes the production of oxygen from H_2O_2 to improve the hypoxic condition of the tumour microenvironment, which facilitates better photodynamic therapy. This "all-in-one" nano-enzyme integrates multiple therapeutic modalities, computed tomography and magnetic resonance imaging properties, and shows excellent therapeutic properties for tumour treatment. However, although carbon nanomaterials have improved therapeutic targeting and efficacy, issues such as solubility and bioavailability remain to be addressed. Looking ahead, the use of carbon nanomaterials in combination with phototherapy and immunotherapy is undoubtedly an inevitable hot direction in the field of cancer therapy research, which needs to be further explored by researchers in order to overcome the existing problems and bring new hope for cancer treatment.

3.3 Applications of carbon nanomaterials in the field of rehabilitation

In addition, the application of carbon nanomaterials in tissue engineering has been a hot research topic in recent years. Tissue engineering is composed of three basic elements: biomaterial scaffolds, seed cells, and a favourable external environment. The unique mechanical, electrical and optical properties, as well as chemical composition and physical properties of carbon nanomaterials make them the reinforcement materials in various scaffolds in tissue engineering, or the carriers for targeted loading of seed cells into specific tissue systems, and they can also provide microenvironments similar to those of biological extracellular matrices. Therefore carbon nanomaterials as new Therefore carbon nanomaterials as new biomaterials have great potential in tissue engineering, and research in cardiac tissue engineering and neural tissue engineering is increasing year by year. A series of studies related to cardiac tissue engineering in recent years have shown that the incorporation of carbon nanomaterials into tissue scaffolds can improve the electrical coupling of cardiomyocytes, the compression modulus of the scaffolds, as well as the maturation and proliferation of cardiomyocytes. The study of Shin et al[29] also supports that scaffolds containing carbon nanomaterials can enhance the differentiation and proliferation of cardiomyocytes, and that cardiomyocytes cultured in the scaffolds based on carbon nanomaterials have the ability to have viability and adhesion. Wu et al [30] found that the scaffolds containing carbon nanomaterials could enhance the adhesion of cardiomyocytes, but the viability of cardiomyocytes was not increased. It was further observed that the morphology of cardiomyocytes cultured on coated glass substrates containing carbon nanomaterials was improved, with the formation of distinct membrane segregation and bridging particles. Neurotissue engineering field Current research related to carbon nanomaterials focuses on the repair and regeneration of diseased neural tissues and stimulation of neural cell growth applications. Tupone[31] and others functionalised graphene oxide with chitosan to form a composite hydrogel with collagen chitosan attached to the surface, which was shown to be beneficial for

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neuronal growth and differentiation. In addition to promoting neuronal differentiation to replace damaged tissues, graphene-based nanosheet materials can also be used directly as electrodes to stimulate nerve regeneration. Feng et al [32] wrapped graphene onto conductive nanofibre scaffolds, and accelerated primary neuronal proliferation and differentiation was achieved in neuronal cells cultured under electrical stimulation. Yan et al have used a similar approach in the restoration of optic nerves, and similarly achieved good results.

Graphene and its derivatives such as graphene oxide, reduced graphene oxide, as representative 2D nanomaterials with excellent mechanical properties, large specific surface area, good electrical conductivity and biocompatibility, are considered to have great potential for bone tissue engineering applications. Reduced Graphene Oxide (RGO) combined with bioceramics (e.g., hydroxyapatite, HA) can effectively improve the performance of bone tissue engineering scaffolds [33]. Studies have reported that RGO doped into porous HA as well as Shape Memory Polyurethane (SMPU)/HA/argininyl-glycyl-d-aspartic acid (RGD peptide) composites were synthesised as novel nanocomposites to enhance the adhesion of their mesenchymal stem cells and to promote the formation of new tissues and their integration with the surrounding bone tissues [34-35]. In addition, it was compared the osteogenic potential of graphene oxide sheets/collagen scaffolds with collagen scaffolds as a control. As graphene oxide had more oxygen-containing functional groups providing it with more active sites, the adhesion with collagen was enhanced, further promoting the proliferation, migration and osteogenic differentiation of MSCs. Although graphene-derived structures have the property of promoting osteogenic differentiation of MSCs, a large amount of clinical trial data is still needed to ensure the safety and efficacy of the graphene-derived structures to be widely used in bone tissue engineering.

4. Conclusion

This paper provides a comprehensive review of the research applications of carbon nanomaterials in the biomedical field. Carbon nanomaterials show unique advantages from disease diagnosis, treatment to rehabilitation. In disease diagnosis, they have high sensitivity and specificity, and can accurately detect biomarkers. In the therapeutic field, carbon nanomaterials' good biocompatibility, deep tissue diffusion, and photothermal conversion ability, etc., bring a new way for the treatment of cancer and other diseases. In the rehabilitation phase, tissue engineering applications as well as neural regeneration applications are the most widespread, with potentially positive effects for other areas as well. However, there are still some challenges, such as long-term stability in vivo, safety effectiveness and other issues to be solved. However, with the deepening of research, new methods and technologies are emerging, providing opportunities for the breakthrough of carbon nanomaterials in biomedical fields. It is hoped that this paper can provide relevant researchers with a comprehensive understanding of the current status of their applications and help determine the direction of scientific research and applications.

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