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REVIEW ARTICLE

Carbon Dot Nanoparticle-based Therapeutic Approaches in Major Neurological Disorders

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Abstract: Neurological disorders (NDs) are diseases that arise due to deformities mainly in the central nervous system (CNS) and also affect the nerves throughout the human body. NDs, including Alzheimer's disease (AD), Parkinson′s disease (PD), Multiple Sclerosis (MS), and a variety of brain malignancies, pose a major healthcare challenge and are the main cause of mortality on the global scale. There are very limited treatment options for the majority of the NDs, and the currently available drugs commonly fail to penetrate the BBB and deliver the drug to the target effectively. These challenges have necessitated the advent of new drug delivery methods that can cross the BBB with ease and deliver the drug by accurately targeting the diseased area in a safe and biocompatible manner. Nanoparticle-based drug delivery strategies offer significant advantages in BBB penetration and drug delivery due to their unique properties. Carbon dots, among nanoparticles with a size below 10 nm, are highly biocompatible, fluorescent molecules that offer ease of functionalization, drug conjugation, and effective detection within biological systems. The literature is rich in reviews on the synthesis, characterization, and application of CDs. However, a review specifically focused on the therapeutic potential of CDs in major NDs is missing. This review aims to fill that gap by presenting a detailed account of the carbon dot-based therapeutic approaches in the treatment of major NDs. It briefly discusses the properties of CDs, the main routes of synthesis, major raw materials, and key synthesis parameters that affect their properties, while placing a greater emphasis on their therapeutic potential. The review provides a detailed assessment of literature from the past 15 years on the development and current challenges in the application of CDs as therapeutic and drug delivery agents. Our analysis reveals that limited research has been conducted on CD-based therapeutics in NDs, particularly in MS and brain tumors, where original research is scarce. This review article highlights the major developments in the therapeutic uses of carbon dots in NDs, addresses a critical research gap, and provides a comprehensive overview of various studies related to carbon-dot-based therapeutic approaches for major NDs.

Keywords: Alzheimer's disease, brain tumor, carbon dots, multiple sclerosis, nanoparticles, neurological disorders**,** parkinson's disease, carbon dots.

1. INTRODUCTION

Neurological disorders (NDs) are conditions arising from disturbances, primarily in the central nervous system (CNS), which consists of the brain and spinal cord, and sometimes also affects the peripheral nerves throughout the human body [1]. The biochemical, physiological, or electrochemical abnormalities in the CNS and peripheral nervous system can have a deleterious effect on the function of the brain, spinal cord, and neurons in the human body [2, 3]. These changes can induce the development of various inflammatory and devastating conditions with an array of symptoms, including loss of sensation, poor neuro-muscular coordination, pain, loss of sensation, alterations in the subconsciousness level, paralysis, confusion, muscle weakness, seizures, and even death [4].

These disorders, being considered as major healthcare challenges and the main cause of mortality at the global level, include Alzheimer's disease (AD), Parkinson′s disease (PD), spinal cord injury, frontotemporal dementia, Prion disease, and a variety of brain tumors [5]. NDs require an intensive patient care regimen involving hospital care, sup-

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portive medical prescriptions, personal care, regular monitoring, and counseling [6]. The lack of specific and accurate treatment options has made NDs a challenging and high-cost disease to manage. Although commonly grouped as NDs, each disease has a different pathophysiology. Some NDs are associated with memory loss and cognitive impairments, while others interfere with the individual's neurological functions including movement, speaking, breathing, and coordination. Most CNS disorders are characterized by disease progression with poor diagnosis, treatment, and recovery [7].

AD, one of the most common causes of dementia, is a progressive neurodegenerative disorder. The loss of basal cholinergic neurons in the forebrain leads to the death of basal forebrain cholinergic neurons due to the anomalous accumulation of abnormal proteins, which also serves as a histopathological marker of the disease [8]. As roughly 80% of these neurons are destroyed, cognitive function deteriorates beyond the brain's compensatory capacity [9]. The condition is characterized by widespread neuronal loss, synaptic breakdown, and the formation of amyloid plaques, which result from the aggregation of amyloid peptides [10]. A key diagnostic indicator of Alzheimer's is the presence of filamentous structures composed mainly of hyperphosphorylated tau protein and neuropil threads.

Parkinson's disease (PD) is a prevalent neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons primarily within the substantia nigra pars compacta and the basal ganglia circuitry [11]. A key pathological hallmark of PD is the presence of intraneuronal inclusions known as Lewy bodies, which are composed predominantly of misfolded, eosinophilic α-synuclein aggregates [12]. These inclusions disseminate across various brain regions, contributing to widespread neurodegeneration and functional impairment. Although the precise etiology of PD remains elusive, it is believed to involve a multifactorial interplay of pathogenic mechanisms, including aberrant protein folding and aggregation, disruption of blood-brain barrier (BBB) integrity, chronic neuroinflammatory responses, and oxidative stress mediated by reactive oxygen species (ROS) [12, 13].

Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system characterized by autoreactive lymphocyte-driven demyelination and axonal degeneration, primarily affecting the white matter of the brain and spinal cord [14]. The disease arises from a complex interplay between genetic susceptibility, particularly within the HLA-DRB1 locus, and environmental factors such as vitamin D deficiency, limited UVB exposure, Epstein-Barr virus (EBV) infection, and lifestyle changes like smoking and alcohol use [15, 16]. Clinically, it presents with a wide spectrum of symptoms depending on lesion location, including visual disturbances (optic neuritis), motor weakness, spasticity, sensory deficits, gait imbalance, fatigue, and cognitive impairment [17].

Brain tumors, or intracranial neoplasms, are highly heterogeneous malignancies arising from the uncontrolled proliferation of central nervous system (CNS) cells [18]. Classified by the WHO from grade 1 to grade 4, their severity ranges from slow-growing, resectable tumors to aggressive forms like glioblastoma. Glioblastoma (grade 4) is the most lethal, marked by rapid growth, invasion, and recurrence, with limited survival despite multimodal treatment [19]. Current therapeutic interventions, including surgery, radiotherapy, and Temozolomide-based chemotherapy, face challenges due to blood-brain barrier (BBB) permeability, tumor heterogeneity, poor drug bioavailability, and rapid recurrence.

The blood-brain barrier (BBB), which is composed primarily of capillary endothelial cells and regulates the movement of molecules across the brain tissues, not only protects the brain from harmful chemical substances and pathogens but also presents a difficulty in the delivery of the majority of pharmaceuticals [4, 20]. There is no specific treatment option against the majority of NDs, and these are considered incurable disorders as the currently available drugs and therapeutics fail to breach the BBB and deliver the drug to the target with curative efficacy. While it is assumed that small molecules can easily cross the BBB, experimental data show otherwise; in reality, only a small percentage (2-5%) of smaller molecules can make it through [21, 22]. Considering the challenges imposed by BBB and the poor efficacy of currently available therapeutics, there is an urgent need to develop therapeutic delivery options that are highly efficient in crossing the BBB and delivering therapeutics to their target in the brain [20]. The advent of nanotechnology and nanoparticle-based drug delivery systems has drawn much attention from the research community due to the advantages associated with the unique properties of nanoparticles [23, 24]. The small size, high surface area to volume ratio, ease of functionalization, and high diffusion potential make these nanoparticles a suitable candidate for drug delivery approaches targeting the BBB [25, 26]. Furthermore, these nanoparticles can be functionalized with the ligand of choice for more specific targeting, and a more controlled release of drugs can be attained [27, 28]. A wide range of nanoparticles, including inorganic metal nanoparticles, carbon dots, liposomes, micelles, and carbon nanotubes, has been employed as nanocarriers for the delivery of drugs and pharmaceuticals [28].

Since their accidental discovery in 2004, while purifying the single-walled carbon nanotubes (SWCNTs), the role of carbon dots (CDs) in NDs was largely unknown and unexplored until the last decade. One of the early studies on the use of CDs in NDs was published in 2014, when Ruan *et al.* [29] synthesized fluorescence CDs through a one-step synthetic process for non-invasive imaging of gliomas. There has been a constant increase in the use of CDs to explore the theranostic potential of CDs in NDs. The objective of this review is to provide a focused and constructive critical assessment of the existing literature on the therapeutic applications of carbon dots (CDs) in major neurological disorders over the last 10-15 years. This review uniquely centers on the role of CDs in therapeutic strategies and drug delivery systems targeting the central nervous system (CNS) to combat major NDs. The review provides a concise overview of the pathophysiology, hallmark symptoms, and underlying mechanisms of these neurological diseases to establish a basic understanding of NDs. It then examines the basic properties of CDs, routes of synthesis, raw materials, and surface properties of CDs, highlighting how specific synthetic pa-

rameters influence their biological activity, followed by a critical assessment of current research studies that explore the use of CDs in neuroprotection, anti-inflammatory action, antioxidant therapy, and targeted drug delivery. By evaluating the global progress in this emerging field, this review aims to identify existing knowledge gaps, highlight promising therapeutic avenues, and offer insights for advancing the clinical translation of CD-based nanotherapeutics in NDs. The following and subsequent sections of this review focus on the properties, synthesis, and role of a specific type of carbon-based nanoparticles, known as carbon dots/carbon quantum dots (CDs/CQDs), in drug delivery approaches for treating various neurological disorders.

2. METHODOLOGY

Peer-reviewed literature up to 2025 was retrieved from electronic sources, including PubMed, Scopus, EMBASE, Ovid, and Google Scholar, for a comprehensive assessment of research work in the area of CD-based therapeutics for NDs. Only original and peer-reviewed articles strictly dealing with the therapeutic potential of CDs within the scope of this review were considered. Articles describing the therapeutic potential of other forms of nanoparticles were excluded.

The literature search was conducted using a combination of the following keywords.

a) “Carbon dots/ Carbon quantum dots or CDs/CQD”.

b) “Neurological disorder” or “Neurodegenerative disorders”.

c) Alzheimer’s disease,” or “Parkinson′s disease” (PD) or “Multiple Sclerosis” (MS) or “Brain tumors”, or “Glioblastoma” or “Glioma”

d) Therapeutics,” or “Drug delivery,” or “Treatment”

3. CARBON DOTS/ CARBON QUANTUM DOTS (CD/CQDS)

Nanoparticles are particles with a diameter of 10^{-9} m and have numerous advantages, including their small size, high surface area-to-volume ratio, ease of diffusion, and fluorescence properties [30]. These particles can be synthesized through numerous physical, chemical, and biological methods; however, green synthetic methods have an edge over others due to their fewer side effects. These nanoparticles show remarkable penetration ability and have been shown to cross the BBB due to their small size [31]. Their further functionalization and surface modifications with a targeting ligand or drug of choice make them a robust tool for drug delivery applications.

Among nanoparticles, carbon dots/carbon quantum dots (CDs/CQDs) have garnered significant interest over the last decade due to their unique properties. Carbon-based nanomaterials with zero dimensions, known as CDs, were initially produced accidentally in 2004 during the purification of single-walled carbon nanotubes (SWCNTs) [32]. Carbon nanotubes (CNTs) are unique structures with a large surface area and chemical stability [33]. CNTs also exhibit good conductivity and electrocatalytic activity, making them more suitable as a support material for electrocatalytic applications than for drug delivery due to their low aqueous solubility, need for functionalization, and low fluorescence. These CDs are small, spherical particles with a size range of less than 10 nm [34]. They have shown negligible toxicity, high penetration, amphiphilic nature, high drug loading, enhanced fluorescence, Photoluminescence (PL), and a low synthesis cost. These properties make CDs an ideal candidate for CNS-based theranostics [18]. CDs, due to their unique properties, have garnered significant attention from researchers across various fields and are being extensively studied in multiple areas, including bioimaging [35], drug delivery [36, 37], biosensing applications [38], solar cells, and catalysis [39, 40].

CDs, unlike carbon nanotubes and fullerenes, have high aqueous solubility and fluorescence in the visible regions. Most CDs are composed of particles with sizes below 10 nm and have sp2/sp3 hybridized graphite (carbon) cores, featuring a variety of functional groups on their surface [41, 42]. The presence of oxygen-containing functional groups, such as carboxyl (-COOH) and hydroxyl (-OH), contributes to the water solubility, fluorescence properties, and colloidal stability of CDs [41-44]. The unique properties of the CDs and their strong variation in color are primarily dependent on their size, which is related to the phenomenon of quantum confinement and surface plasmon resonance (SPR) [45]. The intrinsic fluorescence of CDs, arising from SPR, their biocompatible nature, stability, safety, and ease of synthesis, makes them highly useful tools in biological applications such as drug delivery, nanomedicine, *in vivo* imaging, and biosensors [46, 47].

3.1. Synthesis of CDs

Synthesis of CDs or any other form of nanoparticle can be broadly divided into two broad categories: 1) the top-down approach and 2) the bottom-up approach.

3.1.1. The Top-Down Approach of CD Synthesis

In the top-down approach, the idea is to physically and chemically generate CDs from a carbon source, which is cleaved, broken down, and exfoliated to produce CDs of a desired size range [35, 48]. This method relies upon the use of carbon sources with sp2 hybridization and with negligible effective energy gaps or band gaps. Methods such as acidic oxidation, arc discharge, and laser ablation are a few popular top-down methods that are used for the large-scale production of carbon dots. These methods often pose problems in terms of uniform size, shape, functionality, and cost [49-51].

3.1.2. The Bottom-up Approach of CD Synthesis

The “bottom-up” approaches of CD synthesis rely upon the use of biological or chemical precursors under ambient temperature and pressure conditions. Many small chemical molecules, such as glucose, citric acid, acetic acid, polyethylene glycol, urea, sucrose, and plant-derived materials like seed extracts and leaf extracts, can be used for the synthesis of CDs *via* bottom-up approaches. The properties of CDs, such as structure, size, fluorescence, and surface functionalization, are dictated by the nature of the starting material (Chemical or biological precursors) [52, 53].

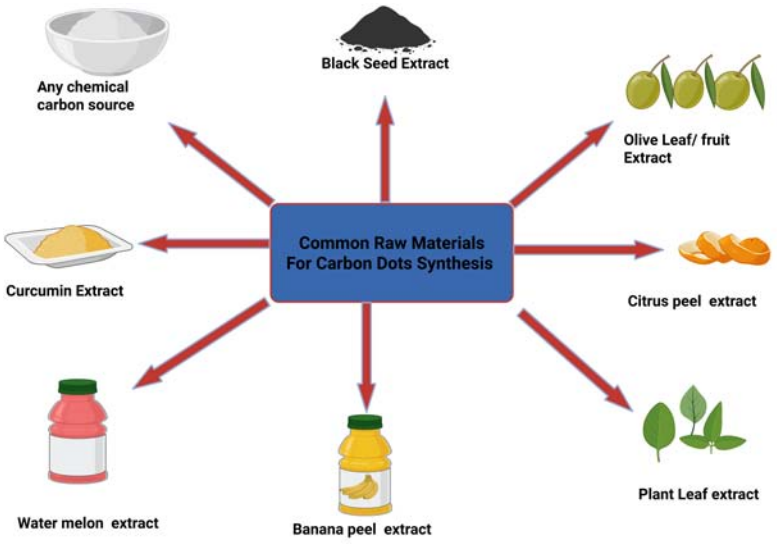

Fig. (1). Representing the common raw materials used in the synthesis of CDs. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

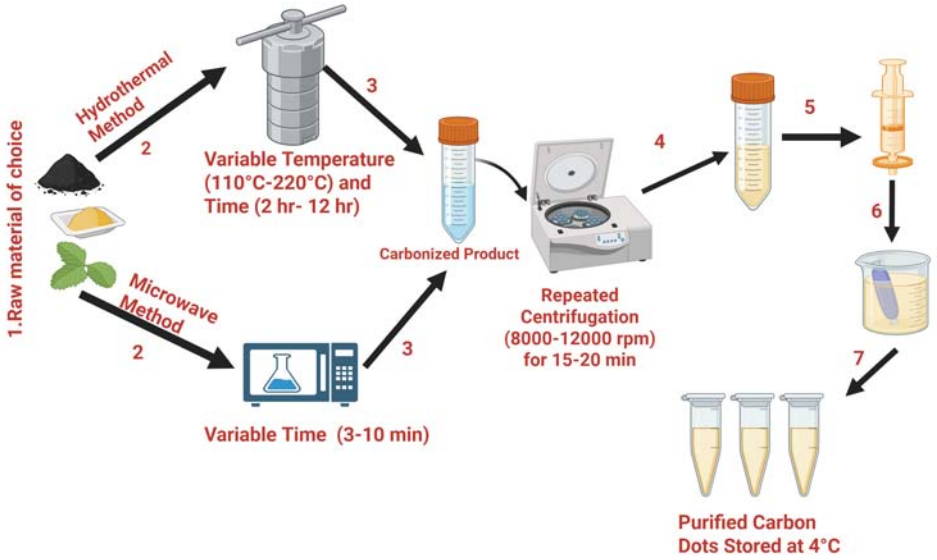

Fig. (2). Showing the most common methods of synthesis and purification of CDs; **1**) Selection of raw materials based upon the availability, cost and application, **2**) Raw material is subjected to either a hydrothermal reactor (operated at different temperature and time conditions) or microwave for desired time (normally 3 to 10 minutes), **3**) The mixture is cooled down & centrifuged repeatedly for clear liquid, **4**) Supernatant is collected, **5**) The mixture is filtered *via* 0.22 µm syringe filter, **6**) The obtained mixture is dialyzed *via* suitable molecular weight cut off membrane (0.5kDa to 3.5kDa, normally), **7**) Obtained product is collected and stored for further application. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

While there is only limited flexibility in controlling these parameters *via* top-down approaches, bottom-up approaches, through the possible modification and alteration of synthesis parameters (temperature, pressure, time, and composition of the constituents), provide sufficient room to synthesize CDs with desired and optimal properties for customized biological applications [54-56]. The bottom-up methods of CD synthesis include carbonization, the hydrothermal method, and microwave-assisted synthesis methods, which are not labor-intensive, involve minimal cost, and allow for a comparatively easier and laboratory-friendly environment. Since this review primarily focuses on the therapeutic application of CDs in neurological disorders, it does not provide an in-depth coverage of synthetic approaches. However, a summary of various synthetic approaches and common raw materials for CD synthesis is provided in Table **1** and Fig. (**1**), respectively. Fig. (**2**) illustrates the most common methods for the synthesis and purification of CDs.

The choice of raw materials, synthesis routes, and use of dopants influence the size, shape, and surface properties of CDs, which in turn impact their biological and therapeutic

Table 1. Summary of raw materials and methods of CD synthesis.

Starting Material	Synthesis Strategy	Size (nm)	Reference
Ascorbic acid	Ultra sonication	3-4	[60]
Glycerol	Microwave irradiation	5	[61]
Xylose	Microwave irradiation	1.8	[62]
Citric Acid and Polyamine	Microwave	5	[63]
Chitosan	Hydrothermal	2	[64]
Hydroquinone	Solvothermal	16	[65]
Watermelon peel	Hydrothermal	2	[66]
Triammonium citrate	Microwave	6.5	[67]
Branched PEI	Crosslink immobilization	63	[68]
Ethyleneglycol bis-(2-aminoethyl ether)-*N*,*N*,*N′*,*N′*-tetraacetic acid and Tris(hydroxymethyl)aminomethane	Thermal carbonization	5	[69]
Melamine	Solvothermal	4–10	[70]
Potassium peroxydisulfate, *N*,*N′*-methylenediacrylamide, AIBN	Hydrothermal	4.56	[71]
Citric Acid and Terbium (III) nitrate pentahydrate	Carbonization	3	[72]

functions. A variety of raw materials and precursors can be utilized for the synthesis of CDs, generating high-quality CDs with a low production cost, ease of synthesis, and minimal use of harmful and toxic chemicals [57]. Therefore, it is highly imperative to consider synthetic parameters, choice of raw materials, particle size, and surface properties while designing and synthesizing CDs for any intended therapeutic application. The Starting material strongly influences the elemental composition and presence of various intrinsic functional groups, which not only decorate and modify the surface of CDs but also affect their biological and biochemical functions [58]. The introduction of green synthetic approaches has enabled the synthesis of CDs in a streamlined process, eliminating the need for lengthy experimental setups and expensive materials. The idea of producing highly fluorescent CDs *via* a simple and environmentally friendly method was first proposed by Li *et al.* [59], who created CDs through a single-step process involving the electrochemical treatment of ethanol and sodium hydroxide.

These CDs exhibited high fluorescence, pH sensitivity, stability, and solubility in water. The water solubility, pH sensitivity, and fluorescence of CDs are desirable properties for any intended drug delivery application across the BBB. Similarly, a large variety of precursors, such as ascorbic acid [60], glycerol [61], xylose [62], citric acid [63], chitosan [64], hydroquinone [65], and watermelon peel [66], have been utilized to produce inexpensive and highly biocompatible CDs.

One of the crucial factors in CD-based therapeutic and bioimaging approaches is the quantum yield (QY) associated with fluorescence [73]. The factors that modulate the quantum yield (QY) of CDs are primarily the particle size, nature, and extent of doping, as well as the presence of functional groups [74]. To control CD fluorescence and add functionalities, heteroatom doping with a suitable dopant is incorporated during the synthesis of the CDs. Nitrogen doping with N-rich precursors, amino acids, and urea, *etc*., is the most widely practiced doping technique to achieve a desirable photoluminescence and QY [47, 75]. Guo and Zhao demonstrated the synthesis of highly stable, water-soluble N-doped CDs using diethylenetriamine as a nitrogen source and citric acid as both a precursor and carbon source. The resulting CDs demonstrated a blue emission spectrum with a very high quantum yield of 84.79% and high photo stability [76]. Nitrogen doping was also performed by Guo *et al.* [77] to synthesize red-emitting, BBB-penetrating CDs for the treatment of PD.

The method of synthesis dictates the surface functionalities of CDs, which are mostly rich in oxygen-containing functional groups, including hydroxyl, carbonyl, epoxy, carboxylic acid, and epoxy ether. These functional groups result in the formation of emissive state traps, known as defects or surface states. For example, Jiang *et al.* synthesized multicolor-emitting CDs through a mixture of tartaric acid and o-phenylenediamine or m-phenylenediamine to obtain blue to green and yellow-green to red emissions, respectively [78]. Red emission can be attributed to the formation of surface states as a function of an increased degree of oxidation and the presence of carboxyl groups with the addition of tartaric acid to a mixture of different isomeric forms of phenylenediamine [79]. The role of temperature is also crucial in obtaining the red shift in the emission of CDs [79], size, and QY of CDs [80, 81]. Zhang *et al.* [82] reported a significant change in the fluorescence intensity of CDs due to an increase in hydrothermal temperature.

The particle size is not only crucial for crossing the BBB but also in the renal clearance of the particle from the biological system, as it minimizes the chronic toxicity of CDs. Tian *et al.* [83], synthesized nickel and nitrogen doped water soluble CDs photothermal transduction agents (PTAs) with the ability of renal clearance and NIR-II absorption. TEM analysis revealed a uniform particle size with an average of 4.6 nm, and the PTAs were found capable of photoacoustic imaging (PAI), multimodal photothermal imaging (PTI), and T_1-weighted magnetic resonance imaging (MRI)-guided photothermal therapy in *in vitro* (HeLa cell lines) and *in vivo* mouse model. These unique nickel and Nitrogen co-doped CDs demonstrate a very strong antitumor and bioimaging potential, and it would be very interesting to exploit their potential in bioimaging and anti-tumor therapy in brain tumor models, especially glioblastoma.

3.2. CDs Mediated Penetration of BBB

The major obstacle in the delivery of therapeutics in NDs is the BBB. While the BBB operates primarily as a barrier between the brain and the rest of the systemic circulation, maintaining the integrity and homeostasis to protect the brain, it also reduces the transport of various drugs and pharmaceuticals [84]. Treatment of various NDs suffers from a major setback where drugs are not able to effectively cross the BBB, which necessitates the development of drug delivery strategies that can overcome the BBB to deliver the drug with enhanced efficacy [85]. As previously discussed, NPs possess an excellent ability to cross the BBB and deliver the payload in varying amounts, depending on their shape, size, and surface properties. It is reported that 98% of small molecules and almost all large molecules fail to cross the BBB, thereby narrowing the probability of current therapeutics crossing and delivering the payload into the CNS across the BBB [86]. Despite this, multiple studies have reported the role of non-functionalized and surface-modified CDs in crossing the BBB [87, 88].

Ruan *et al.* [29] studied the accumulation of glycine-derived CDs (CD-Gly) in BBB penetration and glioma tissue accumulation. They reported a higher fluorescence intensity in the brain of tumor-bearing mice compared to the normal brain, showing the ability of CDs in BBB penetration. Similarly, Seven *et al.* [89] reported the use of glucose-derived CDs to exploit the overexpressed glucose receptors (GLUT1) on the BBB. The CDs were surface-functionalized with fluorescein to develop conjugated CDs (GluCD-F) for BBB penetration and drug delivery in two subsequent *in vivo* BBB models of rats and zebrafish. The study reported an increased accumulation of GluCD-F in the central canal in line with their transport across the BBB, following the injection into the zebrafish heart. Intravenous injection in experimental rats resulted in the accumulation of CDs in the CNS and neurons, with the most significant accumulation occurring in the grey matter of the cervical spinal cord. The BBB penetration of CDs was also assessed by Mintz *et al.* [90]. They synthesized tryptophan-based CDs by utilizing urea and 1,2-ethylenediamine (EDA) as doping agents. CDs were reported to cross the BBB in the zebrafish model *via* transport-mediated endocytosis by effectively utilizing the large amino acid transporter 1 (LAT1). LAT1 targeting was also exploited by Li *et al.* [91] to achieve BBB penetration by CDs. The authors synthesized Large Amino Acid-Mimicking (LAAM) CDs exhibiting multiple functional groups capable of BBB penetration, targeted drug delivery, and brain tumor imaging in an experimental mouse model. The use of transferrin and angiopep-2 conjugation for BBB targeting has also been reported previously [92, 93].

4. ROLE OF CDS IN THE MANAGEMENT OF NDS

4.1. Role of CDs in AD Therapeutics

AD is one of the most common forms of NDs, responsible for more than 80% of global dementia cases [94]. It is a neurodegenerative disease affecting the brain and is characterized by brain damage, loss of cognitive function, loss of learning ability, and progressive behavioral, mental, and functional abnormalities. The aggregation of amyloid beta (Aβ) plaques and the formation and accumulation of neurofibrillary tangles (NFTs) in the brains of affected individuals are well-known signs of AD [95]. A general mechanism of AD pathogenesis was shown in Fig. (**3**). Most of the approved therapeutics exert their therapeutic action by regulating the activity of enzymes and neurotransmitters. These therapeutics suffer from low bioavailability, poor aqueous solubility, and inability to cross the BBB and therefore remain insufficient to cure the diseases completely, necessitating new drug development and delivery methodologies [96, 97].

Due to the numerous associated advantages, a wide range of NPs (Metal NPs, Lipid NPs, and CDs) have been investigated for the treatment of AD [98]. The CDs are gaining much popularity in BBB penetration and drug delivery because of their ability to cross the BBB, non-toxicity, ease of functionalization, high drug loading, and release capacity *etc*.

Aggregation of tau protein results in the formation of NFT, a classic hallmark of AD. Zhang *et al.* [87] utilized two types of CDs for inhibiting tau protein aggregation to tackle AD. The CDs, namely carbon nitride dots (CNDs) and black carbon dots (B-CDs), were conjugated with memantine hydrochloride (MH) and subsequently tested *in vivo* in a zebrafish model. The results demonstrated that CDs were able to cross the BBB and B-CDs, with or without conjugated MH, and efficiently inhibited the aggregation of tau protein.

Chung *et al.* [99] used CDs to suppress the extracellular deposition of Aβ peptide aggregates, which is another hallmark of AD. They developed red light-responsive, aptamer-functionalized CDs to target and suppress Aβ aggregation both *in vivo* and *in vitro*. Red light-driven photomodulation mediated a remarkable reduction in Aβ in 5x FAD transgenic mice co-expressing five familial AD mutations, and it reduced the burden by 40% compared to untreated brain hemispheres. In another study by Chung *et al.* [100], ammonium citrate-derived CDs functionalized with branched polyethyleneimine (bPEI) were used to effectively suppress Aβ self-assembly and break β-sheets, thereby attenuating Aβ aggregation and preventing disease progression. The results demonstrated that conjugated CDs with cationic properties

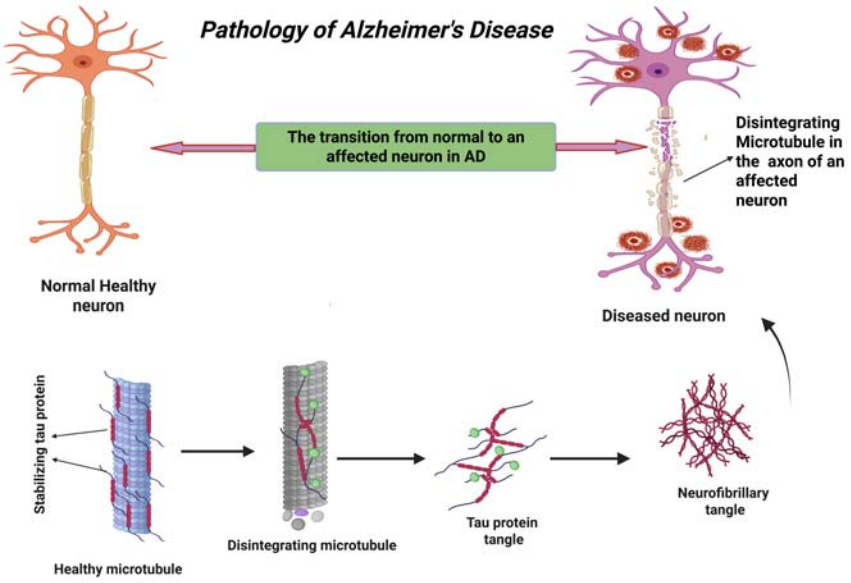

Fig. (3). Illustrates the general mechanism of AD pathogenesis, as well as the differences between a normal neuron and an affected neuron with AD. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

strongly interacted with the negatively charged residues of the Aβ peptide, inhibiting its aggregation and subsequent plaque formation, reducing cytotoxicity, and enhancing cell viability *in vitro*.

The selenium-doped carbon quantum dots (SeCQDs) have also been utilized by Zhou *et al.* [101] for inhibiting Aβ self-assembly. The authors utilized large amino acid-mimicking SeCQDs with anti-aggregation and antioxidant properties in a comprehensive study involving both *in vivo* and *in vitro* analysis. The presence of amino and carboxyl groups as functionalized moieties on SeCQDs facilitated multivalent interactions with Aβ, thereby preventing the aggregation of Aβ *in vitro*. Additionally, treatment with CDs reduced reactive oxygen species (ROS) generation and enhanced cell viability compared to cells treated with Aβ aggregates. The intravenous injection of SeCQDs into C57BL/6 mice resulted in enhanced deposition in the brain, demonstrating the ability of these CDs to penetrate the BBB and also improving the memory deficit caused by Aβ peptide aggregation.

In the study by Zhang *et al.* [87], the authors synthesized Congo red-derived CDs from Congo red and citric acid to target the inhibition of Aβ peptide and tau protein aggregation. The three types of CDs, namely CRCD1, CRCD2, and CRCD3, obtained by varying the amount of precursor material, were tested for their potential in inhibiting Aβ peptide and tau protein aggregation. They demonstrated that the so-obtained CRCDs exhibited low cytotoxicity and strong potential to inhibit the aggregation of Aβ and tau proteins. Among these three variants, CRCD3 was reported to have strong potential to cross the BBB in a zebrafish experimental model and inhibit the aggregation of Aβ and tau proteins. This study highlights the significance of using Congo-red-derived CDs as an effective drug delivery agent for neurological disorders.

The neuroprotective effect of verapamil (VRH)-loaded, hyaluronic acid-modified CDs (HA-CQDs) was studied by Mosalam *et al.* [102] in an *in vitro* AD model induced by Aβ in SH-SY5Y and Neuro-2a neuroblastoma cells. VRH is an L-type calcium channel blocker known to possess anti-inflammatory and antioxidant activity [103]. The authors demonstrated that treatment with VRH alone or VRH-loaded HA-CQDs in SH-SY5Y and neuroblastoma cell lines increased the survival of treated cells, mitotic index, and mitochondrial membrane potential. It also caused enhanced gene expression and a reduction in inflammation through decreased ROS generation. However, the effect of VRH-loaded HA-CQDs on the aforementioned parameters was more profound than that of the free VRH alone, demonstrating the potential of HA-CQDs conjugated with VRH in inhibiting amyloidosis.

Wei *et al.* [104] synthesized quercetin (Que) and p-phenylenediamine-derived red-emission CDs as a novel theragnostic agent against AD. The CDs at micromolar concentrations of 2 and 5 μg/mL significantly inhibited the aggregation of Aβ peptide and induced rapid depolymerization of mature Aβ fibrils, respectively. The *in vitro* results demonstrated the further potential of CDs in alleviating Aβ-induced cytotoxicity and an approximately 25% increase in the viability of cultured cells. Also, *in vivo* studies in AD nematodes showed that CD treatment resulted in a 50% enhanced survival. The authors further demonstrated that these CDs were able to selectively identify Aβ plaques *via* red fluorescence imaging, both *in vivo* and *in vitro*.

Yan *et al.* [88] synthesized L-glutamate and 1,2-diaminobenzene-derived red-emitting multifunctional CQDs (RCQDs) as a therapeutic agent for AD. The RCQDs exhibited high affinity for Aβ42 peptides, resulting in a potent inhibition and disaggregation of Aβ42 aggregates, inhibition of oxidative stress *via* ROS scavenging, and enhanced cellu-

lar proliferation and survival. Additionally, the treatment of microglial cells with RCQDs demonstrated their potential in preventing neuroinflammation and Aβ42-induced cytotoxicity. The authors further demonstrated the BBB penetration potential of these CDs through *in vitro* and *in vivo* models, showing the ability of CDs to target the brain in AD treatment.

CQDs functionalized with curcumin (Cur-CQDs) have also been used to inhibit the phosphorylation of tau protein and Aβ by Lim *et al* [105]. Out of four different types of Cur-CQDs, Cur-CQD 210 was found to be highly effective in the inhibition of $A\beta_{42}$ aggregation and tau hyperphosphorylation. It reduced cytotoxicity in human neuroblastoma cell lines SH-SY5Y. The absence of an *in vivo* model to assess the potential of BBB penetration, systemic cytotoxicity of CDs, and changes in overall survival were a few limitations of this study.

In a recent study, Shao *et al.* [106] utilized selenium-doped CDs (Se-CDs) for copper ion chelation, inhibition of Aβ aggregation, and ROS scavenging and neutralization. Authors reported that Se-CDs were highly effective in neutralizing superoxide anions and hydroxyl free radicals, as well as chelating copper ions, thereby preventing Aβ-associated cytotoxicity to neurons. While this study reports a highly effective and distinct category of carbon dots for disrupting amyloid Aβ and scavenging ROS *in vitro*, it lacks suitable *in vivo* studies for further validation. Further *in vivo* studies involving these Se-CDs may offer new avenues in CD-based therapeutics for AD.

4.2. Role of CDs in the treatment of Parkinson's disease

PD is another common neurodegenerative disorder that occurs due to degeneration of dopamine-producing neurons in the substantia nigra and basal ganglia [107]. Another important hallmark of PD progression is the inclusion of abnormal proteins of eosinophilic nature in the affected neurons, known as Lewy bodies [108]. These Lewy bodies get distributed throughout the brain, causing severe neuronal damage and degeneration [109]. The mechanism of Lewy body formation is illustrated in Fig. (**4**), showing the progression from a healthy to a diseased neuron. Part 4a (upper left) depicts a healthy neuron without Lewy bodies, while part 4b (upper right) shows a typical PD neuron with Lewy body deposits, exhibiting neurodegeneration. The exact etiology of PD is not well defined and includes protein misfolding and aggregation, loss of BBB integrity, neuroinflammation, and ROS-dependent damage to the neurons [110]. Several genes have also been implicated in PD, including mutations in parkin, DJ-1, PINK1, and LRRK2, as well as mutations and duplications of the *alpha-synuclein* gene [111, 112]. The PD is characterized by tremors, difficulties in motion, muscle rigidity, and postural instability [113].

In the study by Guo *et al.* [77], the authors synthesized red light-emitting, N-doped CDs with properties that release nitric oxide and quench ROS against PD. The CDs were further modified with lactoferrin and polyethylene glycol to achieve better BBB penetration and target dopamine-releasing neurons. Functionalized CDs contributed significantly to nitric oxide (NO) release, enhanced BBB penetration, and accumulation in the brains of experimental PD mice. The CDs reduced ROS-mediated oxidative stress and inflammatory reactions in the brain and improved behavioral performance in the experimental mice. Overall, this study highlighted the role of these CDs in PD therapeutics and imaging.

The use of Se^{-2}-doped carbon nitride quantum dots (SegCN-QDs) with enzymatic activity was attempted by Zhang *et al.* [114] to address neuroinflammation in PD. SegCN-QDs were loaded with Cordycepin (Cor) for effective BBB penetration and visualized targeted regulation of microglia to degrade α-synuclein for PD treatment. Their results showed that CDs successfully decreased localized hypoxia at the disease site by generating oxygen. The authors further demonstrated that the superoxide dismutase (SOD)/catalase (CAT) activity of the CDs resulted in the conversion of ROS into O_2, which subsequently inhibited the ROS-nuclear factor-kappa B (NF-κB)/NOD-like receptor protein 3 (NLRP3) axis at the disease sites to diminish the inflammatory response. Additionally, the delivery of Cor, conversion of ROS, and oxygen production lead to the mitigation of injury in dopamine-releasing neurons *via* a pronounced decline in α-synuclein in the C57BL/6 mice model *in vivo*.

The accumulation of reactive aldehydes generated through catabolic processes in tissues and cells is associated with PD and may cause potential neuronal damage. One of the prominent aldehyde species generated by the enzymatic catabolism of dopamine in PD is dopamine metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL). This cytotoxic compound generates ROS and promotes the aggregation of presynaptic protein α-synuclein. Bloch *et al.* [115] synthesized lysine-derived CDs, specifically targeting and scavenging DOPAL in PD. *In vitro* studies using SH-SY5Y cell lines demonstrated that lysine-derived CDs could efficiently internalize and inhibit the DOPAL-mediated modification and oligomerization of α-synuclein in a safe and non-toxic manner.

Kumar *et al.* [116] have examined the role of CDs synthesized using quinic acid (QACQDs) and chlorogenic acid (ChACQDs) in protecting against a paraquat-induced model of PD. CDs exhibited biocompatibility and anti-oxidant activity in SH-SY5Y cell lines *in vitro* and protected the treated cells from the neurotoxic impact of paraquat. The authors further demonstrated that the CDs could protect against the loss of dopaminergic neurons in the *C. elegans* model and inhibit the assembly of amyloid-forming proteins. Although this study demonstrated the potential of two distinct types of CDs in neuroprotection, ROS scavenging, and amyloid aggregation in cell culture and the nematode model of C. elegans, further evaluation in more advanced animal models is warranted to examine their ability to penetrate the BBB, provide neuroprotection, and ensure biocompatibility. A summarized pictorial representation of various effects exerted by CDs in the prevention of AD and PD was given in Fig. (**5**).

To overcome the challenges encountered by current PD therapeutics in BBB penetration, fucoidan (FD)- derived CDs were used by Han *et al.* [117] in a recent study. Authors reported that synthesized FDCDs were rich in the SO42- functional group, exhibiting significant antioxidant,

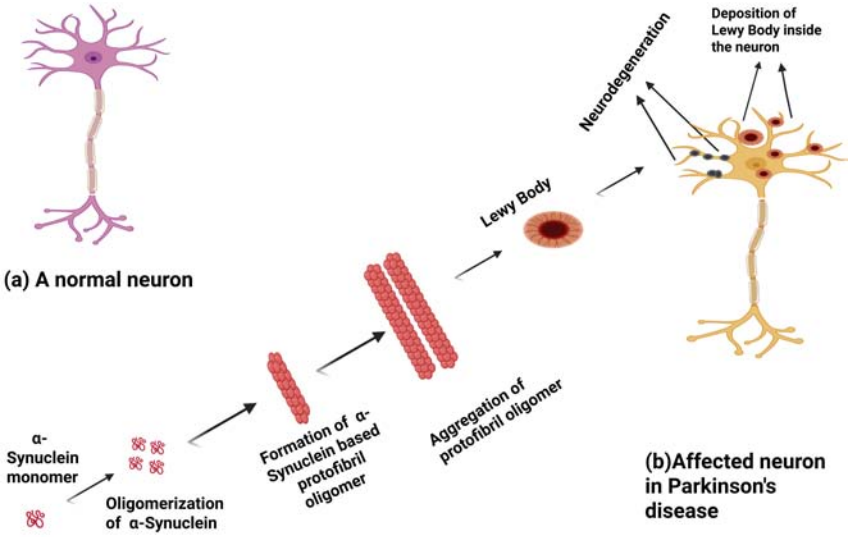

Fig. (4). Shows a normal (**a**) and affected neuron (**b**) in PD along with the basic mechanism of Lewy body formation in the PD pathogenesis, which starts with the oligomerization of α-synuclein, which further gets transformed into an α-synuclein-based protofibril oligomer. These oligomers form aggregates, ultimately leading to Lewy body formation. The deposition of Lewy bodies leads to neurodegeneration and PD symptoms. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

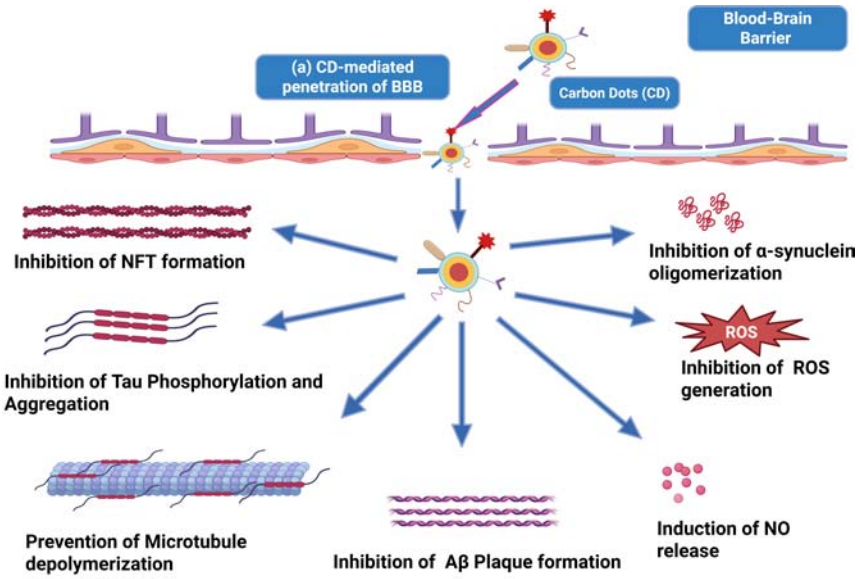

Fig. (5). Showing the impact of CDs on the pathogenesis of AD and PD. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

anti-inflammatory, and anti-apoptotic activity, and mitigating the 1-Methyl-4-phenylpyridinium ion (MPP^+)-induced damage in PC12 cells *in vitro*. The BBB penetration efficiency was analyzed through 3D small animal imaging after intravenous administration. The FDCDs were found to restore motor function in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mice in a safe and non-toxic manner. Further validations regarding the effects of FDCDs on the inhibition of Lewy bodies and alpha-synuclein inhibition, involving a larger animal model, may open new avenues in FDCD-based therapies for PD.

In another recent study, Yang *et al.* [118] utilized Dopamine hydrochloride and 1,2-bis(2-aminoethoxy)ethane (EDBE)-based CDs as an anti-inflammatory agent to alleviate the motor and non-motor symptoms of PD. These polydopamine CDs (PDA CDs) were further encapsulated in macrophage-derived exosomes for improved penetration and uptake. The PDA-CDs were reported to ensure neuroprotec-

tion *via* diminishing inflammation, ROS generation, and α-syn formation. The PDA-CDs not only brought about a significant change in motor function but also impacted non-motor associated functions in PD experimental mice through the recovery of synaptic vessels, mitochondrial protection, and the prevention of α-syn accumulation. Further studies considering the immunogenic challenges associated with macrophage-derived exosomes could further strengthen the role of this novel therapeutic approach in PD.

4.3. Role of CDs in Multiple Sclerosis Therapeutics

Another prominent inflammatory neurological disorder is multiple sclerosis (MS) [119]. It occurs due to the autoreactivity of the immune system against myelinated axons, resulting in the destruction of the myelin sheath and axons [16, 120]. MS is a complex neurological disease with mostly unidentified causes, with some studies reporting the role of many genes in increasing MS susceptibility, while others report the role of vitamin D, exposure to ultraviolet B (UVB) radiation, Epstein-Barr virus (EBV), and lifestyle changes including smoking and alcohol consumption [121]. Although there is no single definitive diagnosis of MS, it is pathologically characterized by the presence of focal areas of demyelination of the white matter of the brain and spinal cord [122].

Unfortunately, throughout our extensive literature survey on various platforms such as Google Scholar, PubMed, and other related platforms, we were not able to find studies regarding the use of CDs in the therapeutics of MS. Few studies regarding the use of other forms of carbon nanoparticles such as graphene and few other non- carbon-based quantum dots have also been reported very sparingly in the treatment of MS.

The first-ever and only study reporting the use of carbon-based graphene quantum dots (GQDs) to inhibit T-cell-mediated neuroinflammation in experimental rats was conducted by Tosic *et al.* [123]. The researchers used GQDs in the Dark Agouti rat model of experimental autoimmune encephalomyelitis (EAE). EAE is an experimental animal model of brain inflammation that exhibits similar symptoms to MS and disseminated encephalomyelitis [124]. The authors demonstrated that intraperitoneal injection of GQD at a concentration of 10 mg/kg of body weight per day for 32 days resulted in enhanced accumulation of GQDs in lymph nodes and CNS of experimental rats *in vivo*, alleviating demyelination of the spinal cord and axonal neurons *via* MAPK/Akt signaling pathway modulation. GQDs also effectively diminished the proliferation and infiltration of reactive Th1 cells and suppressed the levels of TNF-α and IL-1, thereby suppressing neuroinflammation in the CNS and spinal cord.

Additionally, the *in vitro* results demonstrated that GQDs effectively prevented T-cell-mediated inflammatory damage to oligodendrocytes and neurons. This study was the first of its kind, reporting the use of a distinct category of quantum dots called GQDs and also showing the potential of these nanoparticles in MS. Further studies with CDs from various sources, along with suitable drug/therapeutic conjugates, are needed to establish their role in MS therapeutics.

Tosic *et al.* [123] utilized a distinct, non-carbon-based quantum dot, called CdSe/ZnS core/shell QDs, against EAE rats, an experimental animal model of MS. The QDs were further modified with myelin oligodendrocyte glycoprotein peptide (MOG) for enhanced *in vivo* visualization. Self-antigenic peptide MOG-functionalized QDs were found to reduce disease symptoms by 10-fold, expand the regulatory T cell population, and promote tolerance *via* the migration of Treg cells into the CNS to tackle the T_H17 and T_H1 cell-mediated inflammatory response. This was also the first study to report the role of quantum dot-mediated tolerance in an experimental model. However, further detailed studies are needed to confirm the myelin-specific nature of tolerance and to establish a concrete role for such nanoparticle-based therapeutic approaches in tackling MS-type NDs, as well as to study and understand the migration of immune cells.

Luo *et al.* [125] investigated the role of selenium-doped CQDs (Se-CQDs) in enhancing the recovery from secondary spinal cord injury through ROS depletion in a rat model of traumatic spinal cord injury (TSCI) and cell culture. The *in vitro* studies revealed that Se-CQDs were highly biocompatible and exhibited a remarkable protective effect against H2O2-induced oxidative damage in astrocytes, PC12 cells, and N2a cells. The authors demonstrated that the CDs reduced inflammatory response, apoptosis, and astrogliosis in the TSCI rat model *in vivo* by successfully scavenging the ROS, a prominent causative factor in demyelination of the spinal cord and neuronal damage. It also improved the locomotor functions in the experimental animal model. The histopathological data showed that differential treatment with Se-CQDS prevented spinal cord injury and reduced demyelination and infiltration of inflammatory cells. Although this study was not conducted in an experimental MS model, it demonstrated the potential of CQDs in reducing neuroinflammation, inflammatory cell infiltration, and demyelination, as well as neuronal damage. This study can open new avenues in the role of CDs in MS therapeutics. Additionally, some studies directly involving experimental MS models must be conducted to explore the full potential of such CDs in the management of MS.

4.4. Role of CDs in Brain Tumor Therapeutics

Brain tumors are termed as intracranial neoplasms and represent a diverse category of neoplastic growths due to abnormal and uncontrolled proliferation and differentiation of CNS cells. Brain tumors are the major cause of cancer-related deaths in almost all age groups, including children, adults, and the elderly [126]. The general treatment for brain tumors includes surgical interventions, radiotherapy, and adjuvant chemotherapy, which is associated with poor prognosis and rapid recurrence [127]. Brain tumors are a highly heterogeneous and diverse form of cancer classified by the World Health Organization (WHO) as grade 1 to grade 4. Grade 1 tumors exhibit fewer complications and slower proliferation, which can be effectively treated with surgical resection [128, 129]. Low-grade gliomas, classified as grade 2 tumors, are characterized by a low proliferation rate and moderate infiltration potential, and can transform into high-grade gliomas. Grade 2 tumor patients are normally treated *via* surgical resection and have an overall survival rate of

more than 5 years [130]. Contrary to Grades 1& 2, grade 3 tumors are histologically malignant and exhibit rapid proliferation and infiltration. The grade 3 tumor treatment includes adjuvant radiation with or without chemotherapy, resulting in an overall survival of 2-3 years [131]. Glioblastoma or grade 4 tumors are highly aggressive tumors characterized by rapid proliferation, invasion, and high recurrence rates. Despite the intensive treatment involving surgical resection, followed by adjuvant radiotherapy and chemotherapy, the overall survival is very low with high morbidity [132]. Glioblastoma, among brain tumors, is the most fatal one and requires a very aggressive standard of treatment consisting of surgery, radiotherapy, and Temozolomide (TMZ)-based chemotherapy [126]. The efficacy of the current therapeutic approach is limited due to the poor bioavailability of TMZ, high recurrence rate, the presence of the BBB, and tumor heterogeneity [127]. Among the current therapeutic options being explored, the advent of nanomedicine and nanotechnology provides promising and novel drug delivery options against glioblastoma.

CDs, due to their small size and ease of functionalization, which provides the attachment of desired drugs, ligands, and targeting molecules, make them a potent tool in drug delivery to tumors. These CDs exhibit high aqueous solubility, stability, and bioavailability, and demonstrate comparatively higher accumulation of the payload in tumors due to the EPR phenomenon. Their ease of diffusion across various barriers and their easier detection in biological systems due to high fluorescence make them an ideal candidate for theranostic applications. CDs also exhibit extraordinary photocatalytic activity owning to their unique and appropriate bandgap, high electron transfer efficiency, and light responsivity, with a capability to generate photo induced electron-hole pairs for the increased production ROS ($^{\bullet}OH$, $O_2^{\bullet-}$) under the irradiation of suitable wavelength of light could demonstrate their potential in the reduction hypoxia induced tumors [133]. The role of CDs in the management of brain tumors was summarized in Fig. (**6**).

To explore the BBB penetration capabilities of CDs, Lu *et al.* [134] synthesized CDs doped with nitrogen (N-CDs) from citric acid and polyethyleneimine. The monodispersed CDs, with a diameter of 2.6 nm, exhibited minimal cytotoxicity in 293T cells, with a viability greater than 80% compared to the control cells, indicating their potential as a non-toxic and safe drug delivery vehicle and *in vivo* imaging agent. The authors further demonstrated the potential of these CDs in BBB penetration *via* an *in vitro* BBB model consisting of astrocytes and primary rat microvascular endothelial cells. Although this study did not involve drug conjugation to determine the drug-carrying potential of CDs, it was a valuable study that reported the safety, efficacy, bioimaging, and BBB penetration ability of CDs.

In the study by Zheng *et al.* [135], the authors synthesized self-targeting fluorescent CDs from d-glucose and l-aspartic acid (CD-Asp) *via* a simple thermolysis method for brain cancer diagnostics. The results demonstrated that the CDs accumulated efficiently in the treated C6 glioma cells without causing significant toxicity, demonstrating their safety and efficacy. The intravenous administration of CDs in experimental mice showed excellent biodistribution and high fluorescence in the mice's brains, proving the ability of the BBB to be penetrated. This work demonstrates the selective efficiency of CD-Asp in crossing the BBB, advocating the use of CDs for *in vivo* imaging and glioma diagnostics.

Li *et al.* [136] reported the use of transferrin-conjugated CDs for the delivery of doxorubicin in pediatric brain tumors. The transferrin functionalization was aimed at selectively targeting the overexpressed transferrin receptors on tumor cells, enhancing BBB penetration, and minimizing the side effects associated with high doses of doxorubicin. The *in vitro* results showed an enhanced uptake of CD-conjugated doxorubicin-transferrin assembly in multiple pediatric brain tumor cell lines compared to cells treated with doxorubicin alone. This study, although limited by its *in vitro* model, demonstrated the potential of transferrin-doxorubicin conjugated CDs in the targeted killing of cancer cells in a more effective and dose-dependent manner. Furthermore, *in vivo* studies, which are currently lacking in the literature, would have been conducted to explore the BBB penetration and anti-cancer potential of this conjugated system.

A triple conjugated CD system was employed by Hettiarachchi *et al.* [137] to overcome the limitations imposed by dual-targeting systems in glioblastoma cell lines. They conjugated the CDs with TMZ and Epirubicin and functionalized the surface of CDs with transferrin for enhanced uptake by glioblastoma cells. The authors assessed the cytotoxicity and anti-cancer effects of their compound in brain tumor cell lines, including SJGBM2, CHLA266, CHLA200 (a pediatric brain tumor cell line), and U87MG. They reported that the triple-conjugated system was significantly more effective than dual-conjugated CDs–transferrin, drug conjugates without transferrin, and free drugs. While this study suggests a better alternative to double conjugates (CDs and drugs), it did not provide further insight into the mechanism of apoptosis and lacked validation of BBB penetration and bioavailability in an *in vivo* animal model. Relevant *in vivo* studies examining uptake, accumulation, BBB penetration, and toxicity are required to fully explore the potential of this triple-conjugated CD system.

Muhammed *et al.* [138] designed ultra-small CDs supported iron single atom (Fe-CDs) nanoenzymes to target drug-resistant glioblastoma. The authors reported that Fe-CDs exhibited multi-enzyme activities parallel to 6 native enzymes, namely oxidase (OXD), peroxidase (POD), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and thiol peroxidase (TPx), imitating the intracellular antioxidant defense system for the killing of the drug-resistant glioblastoma cells in a ROS-dependent manner. The Fe-CDs were surface functionalized with angiopep-2 to facilitate penetration and transport across the BBB. The functionalized CDs with peptide (Fe-Cds@Ang) induced cytotoxicity, mitochondrial dysfunction, lysosome-mediated autophagy, and apoptosis *via* an elevation in ROS level in treated U251-TR and U87MG cell lines. The *in vivo* studies demonstrated high biocompatibility, penetration of the BBB, and enhanced accumulation within TME, resulting in autophagy-mediated tumor destruction, reduction in tumor volume, and enhanced overall survival in the xenograft mice model. Overall, this study showed the significance of func-

tionalized Fe-CDs in glioblastoma therapy. Further studies regarding its impact on inducing ferroptosis and carrying a chemotherapeutic payload should be conducted in relevant animal models to explore its potential in glioblastoma treatment.

Algarra *et al.* [139] synthesized CDs from 2-acrylamido-2-methylpropanesulfonic acid (AMPS) to determine the potential biocompatibility and drug-carrying efficiency in glioblastoma cell lines. The synthesized AMPS-CDs were further conjugated with the drug Riluzole, and their cytotoxic potential was tested against the glioblastoma cell line. The authors demonstrated that the conjugated AMPS-CDs not only affected DNA but also targeted proteins in the treated glioblastoma cells. Although this study is promising, it lacks further validation of cytotoxicity and anticancer mechanisms through appropriate cell culture and *in vivo* studies. Additionally, the full potential and limitations of these CDs in BBB penetration and drug transport should also be investigated using a suitable *in vivo* model.

Shamsipour *et al.* [140] developed a CDs-based imaging and delivery system to control the issue of the initial burst of Temozolomide payload while minimizing its neurotoxicity in glioblastoma therapy. The authors employed coaxial electrospinning to produce CQDs embedded in core/shell chitosan-polyethylene oxide/carboxymethyl cellulose-polyvinyl alcohol (CS-PEO-CQDs/CMC-PVA) for the effective delivery of TMZ. The results demonstrated a biphasic pattern of TMZ release from the core-shell assembly with a continuous release up to twenty-eight days after the initial burst. *In vitro* studies demonstrated an enhanced cytotoxic activity of CD-TMZ against the free form of TMZ in the U-251 glioblastoma cell line. Although this study presented a novel and distinct approach to CD-based delivery of TMZ, it was limited by further cell culture and *in vivo* studies, failing to explain other valuable aspects of cell death and apoptosis. A further study involving various glioblastoma cell lines and a suitable *in vivo* tumor model is needed to effectively determine and explore the fate of this system in the delivery of TMZ for glioblastoma therapeutics.

The potential of carbon nitride quantum dots (CNQDs) as an effective bio-imaging tool was examined by Liyanage *et al.* [141] for targeted brain tumor therapy. *In vitro* bio-imaging and distribution results demonstrated that CNQDs were able to enter the treated pediatric glioma cells (SJGBM2) preferentially. This study also reported the use of fluorescent imaging to analyze the distribution of CNQDs in the lysosomes of the treated cells within 6 hours after the treatment. Although this work highlighted the potential in bioimaging and distribution, it did not address the therapeutic aspects of glioma treatment. Further conjugation with a suitable chemotherapeutic drug might prove the therapeutic potential of CDs in treating brain tumors.

Liyanage *et al.* [142] studied the potential of non-toxic carbon nitride dots (CNDs) in the selective and preferential targeting of glioblastoma *in vitro*. CNDs were surface-functionalized with transferrin and further conjugated with the chemotherapy drug Gemcitabine to target pediatric high-grade glioma cell line SJGBM2 glioma cells. Its safety and efficacy were also tested in a non-malignant embryonic kidney cell line, HEK293. The conjugated CND assembly was shown to be preferentially taken up by tumor cells, resulting in pronounced cell death (more than 95%) at a 1 μM concentration, whereas 100% viability was reported in treated non-tumor cells, demonstrating its potential for selective cancer targeting *in vitro*. Moreover, the functionalization with transferrin resulted in more pronounced cell death at a 100-fold lower concentration of 10 nM. Furthermore, the CNDs alone and the conjugated CNDs were reported to cross the BBB in the zebrafish experimental model. This study reports the use of the drug Gemcitabine in targeting glioma cells. Further studies elucidating the mechanisms of their effect may provide new insights into the treatment of brain tumors.

To achieve more effective BBB penetration, Li *et al.* [92] functionalized CDs with transferrin. In a zebrafish model, the transferrin-conjugated CDs were tested for their BBB penetration *via* transferrin receptor-mediated endocytosis. The authors concluded that transferrin-coated CDs were capable of CNS entry, while CDs without transferrin could not penetrate it. This study highlights the role of transferrin-mediated BBB penetration but lacks a suitable *in vivo* animal model and detailed cell culture studies to explain the role of transferrin-CDs in drug delivery to brain tumors.

5. CHALLENGES & OPPORTUNITIES

While carbon dots (CDs) have shown considerable promise in preclinical models for neurological disorders, their therapeutic application remains underexplored and fragmented. CDs, due to their diverse synthetic routes and variable surface chemistries, often exhibit a broad range of physicochemical properties, including size, shape, elemental composition, and photoluminescent behavior. However, these characteristics are typically reported using inconsistent methodologies across different studies, making it difficult to compare or validate results. This inconsistency directly affects the reproducibility of CD properties, which is crucial for industrial-scale production, regulatory approval, and quality control. Techniques commonly used for characterization, such as transmission electron microscopy (TEM), X-ray photoelectron spectroscopy (XPS), and fluorescence quantum yield measurements, are technically demanding and financially intensive, limiting their accessibility to only well-equipped laboratories. The absence of harmonized benchmarks not only complicates the assessment of safety and efficacy for biomedical applications but also hinders the formulation of regulatory guidelines. Consequently, despite their promising therapeutic and diagnostic capabilities, CDs remain largely confined to laboratory-scale use, with minimal penetration into the pharmaceutical and biotechnology markets. When it comes to using carbon dots, our analysis of the existing literature reveals a significant underrepresentation of CD-based interventions in diseases like Parkinson's disease (PD) and multiple sclerosis (MS). In the case of MS, no direct studies utilizing CDs have been reported, despite the proven efficacy of non-carbon-based nanomaterials in experimental models, highlighting a compelling opportunity to expand CD research into this area. Similarly, the integration of CDs for delivering temozolomide (TMZ), the standard chemotherapeutic agent for glioblastoma, has been minimally explored, despite CDs having the potential to enhance targeted delivery and pharmacokinetic profiles.

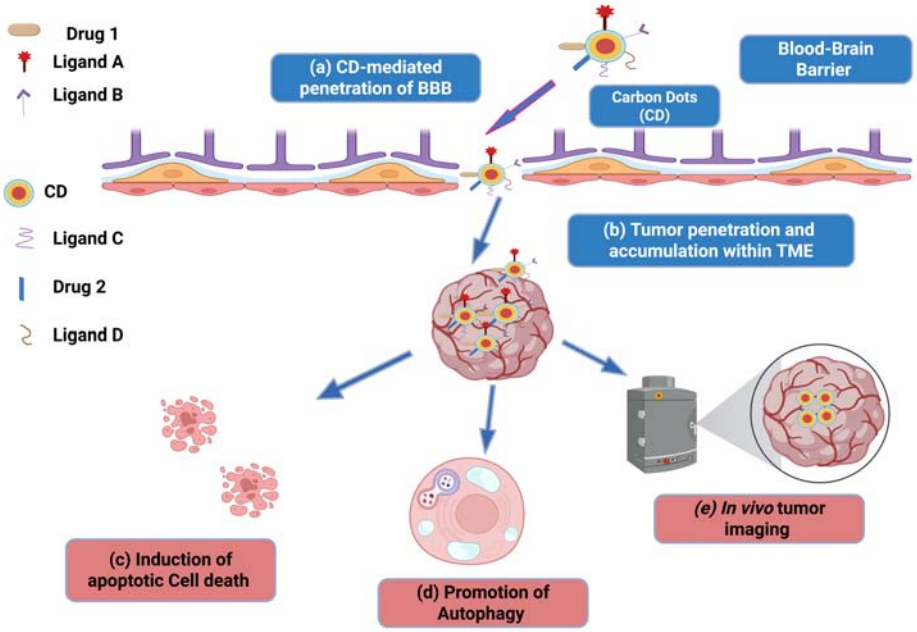

Fig. (6). Showing the role of CDs in BBB penetration, induction of apoptosis, autophagy, and bio-imaging of tumors. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

These gaps highlight a broader issue: the therapeutic potential of CDs in neurological disorders remains largely unexploited. With increasing understanding of the molecular mechanisms underlying neurodegeneration, there is a unique opportunity to improve and utilize the tunable surface chemistry, nanoscale size, and blood-brain barrier permeability of CDs for targeted drug delivery and neuroprotection. However, a dedicated and systemic investigation is mandated to translate these properties into clinically significant outcomes. The current scenario of CD-based research and the prevalence of diseases presents both a significant challenge and a vast horizon of opportunities in CD-based therapeutics. More dedicated research work in this area could potentially enhance the precision and effectiveness of treatment strategies for central nervous system diseases.

CONCLUSION AND FUTURE PERSPECTIVES

Among NDs, disorders such as AD, PD, and MS require an intensive patient care regimen involving hospital care, supportive medical prescriptions, personal care, and regular monitoring due to the lack of accurate treatment. Disorders like brain tumors, including glioblastoma and pediatric gliomas, are characterized by even narrower treatment options with poor survival rates. The increasing prevalence of NDs poses a very tough challenge to global health, necessitating innovative therapeutic approaches. CDs are a specific type of carbon-based nanoparticles and have proven their potential as therapeutic and diagnostic agents in various neurological disorders. These CDs are small, spherical-shaped particles with a size range between 2-10 nm. Their unique properties, such as high biocompatibility, negligible toxicity, enhanced BBB penetration, amphiphilic nature, high drug loading, enhanced fluorescence, Photoluminescence (PL), and low cost of synthesis, make them a highly useful tool in drug delivery and bio-imaging. Also, their ability to cross the BBB, due to small size and high diffusional thresholds, low immunogenicity, high drug loading capacity, and release abilities, makes CDs an ideal candidate for CNS-based theranostics. CDs offer a significant advantage over other forms of nanoparticle-based drug delivery systems, particularly in crossing the BBB, tumor penetration, and high drug accumulation. Additionally, the surface functionalization of CDs with appropriate ligands to effectively target particular types of receptors or proteins, thereby achieving highly specialized therapeutic goals, is relatively easy due to the abundance of chemical moieties.

The CDs have demonstrated their potential in treating NDs by promoting a decrease in the level of inflammatory cytokine secretion, inhibiting Aβ and Tau aggregation, reducing ROS levels, and mitigating injury in dopamine-releasing neurons. Although there are limited studies on CDs in MS, carbon-based graphene quantum dots (GQDs) have demonstrated the ability to attenuate T-cell-mediated neuroinflammation and demyelination in experimental autoimmune encephalomyelitis (EAE) models. Selenium-doped CDs have also demonstrated the ability to mitigate spinal cord injury and demyelination through ROS scavenging, underscoring their potential in MS therapeutics.

In brain tumor and glioblastoma therapy, CDs conjugated with chemotherapeutics and functionalized with transferrin or other targeting peptides have shown potential in selective cytotoxicity to cancer cells and BBB penetration. CDs exhibiting multi-enzyme mimetic activities to promote ROS-dependent tumor cell apoptosis and autophagy also show potential in tumor regression *in vivo*.

There has been significant progress in exploring the therapeutic potential of CDs for Alzheimer's disease (AD).

However, similar investigations in the context of Parkinson's disease (PD) and multiple sclerosis (MS) remain limited. To date, direct studies on the medicinal and therapeutic applications of CDs for MS treatment have been reported only sparingly. In contrast, several studies have demonstrated the efficacy of non-carbon-based quantum dots in experimental autoimmune encephalomyelitis (EAE) models, an established animal model of MS. This disparity in research highlights a critical knowledge gap and presents an opportunity for future studies to develop and optimize CD-based nanotherapeutics for MS and other neurological disorders. Furthermore, temozolomide (TMZ) remains the standard chemotherapeutic agent approved for glioblastoma; however, only a limited number of studies have explored the use of CDs as drug delivery vehicles for TMZ.

Expanding investigations into functionalized CDs for targeted and controlled TMZ delivery may enhance therapeutic outcomes and overcome current limitations in glioblastoma treatment. Further development of CDs with enhanced fluorescence, notably in the NIR range (red emission), can eliminate the need for fluorescence dyes and promote their use as safe and biocompatible imaging and contrast agents. Surface functionalization of CDs with targeting ligands and specific antibodies/nano bodies for targeted drug delivery could become a game changer in the drug delivery applications across the BBB. Additionally, the use of specific ligand-functionalized CDs for tumor bioimaging, such as the conjugation of transferrin, VEGF, and other overexpressed receptors, can open new opportunities in the *in vivo* bioimaging of CNS tumors. Devising reproducible synthetic strategies to produce CDs with desired physicochemical, optical, and biological properties is further warranted to promote the therapeutic potential of CDs in NDs.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: Study conception, literature survey, data collection and analysis, writing the first draft, and figures: MH; Idea, supervision, revision, and final editing: MAH. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
AMPS	=	2-acrylamido-2-Methylpropanesulfonic Acid
Aβ	=	Amyloid Beta
B-CDs	=	Black Carbon Dots
BBB	=	Blood-Brain Barrier
bPEI	=	Branched Polyethyleneimine
CAT	=	Catalase
CD-Asp	=	d-glucose and l-aspartic Acid
CD-Gly	=	Glycine-derived CDs
CD/CQDs	=	Carbon dots/Carbon Quantum Dots
ChACQDs	=	Chlorogenic Acid Carbon Quantum Dots
CNDs	=	Carbon Nitride Dots
CNQDs	=	Carbon Nitride Quantum Dots
CNS	=	Central Nervous System
Cor	=	Cordycepin
CRCD	=	Congo Red-derived CDs
Cur-CQDs	=	Curcumin Carbon Dots
DOPAL	=	3,4-dihydroxyphenylacetaldehyde
EAE	=	Experimental Autoimmune Encephalomyelitis
EBV	=	Epstein-Barr Virus
EDA	=	1,2-ethylenediamine
GluCD-F	=	Glucose-derived Fluorescein Conjugated CDs
GLUT1	=	Glucose Transporter 1
GPX	=	Glutathione Peroxidase
GQD	=	Graphene Quantum Dots
HA-CQDs	=	Hyaluronic acid-Modified CDs
LAAM	=	Large Amino Acid-Mimicking
LAT1	=	Large Amino Acid Transporter 1
MH	=	Memantine Hydrochloride
MOG	=	Myelin Oligodendrocyte Glycoprotein
MS	=	Multiple Sclerosis
N-CDs	=	Nitrogen Carbon Dots
NDs	=	Neurological Disorders
NF-κB	=	Nuclear Factor-kappa B
NFT	=	Neurofibrillary Tangles
NLRP3	=	NOD-like Receptor Protein 3
OXD	=	Oxidase
PD	=	Parkinson′s disease
PL	=	Photoluminescence
POD	=	Peroxidase
QACQDs	=	Quinic Acid Carbon Quantum Dots
Que	=	Quercetin
RCQDs	=	Red-Emitting Multifunctional CQDs
ROS	=	Reactive Oxygen Species
SeCQDs	=	Selenium-doped Carbon Quantum Dots
SOD	=	Superoxide Dismutase
SPR	=	Surface Plasmon Resonance
SWCNTs	=	Single-walled Carbon Nanotubes

TMZ	=	Temozolomide
TPx	=	Thiol Peroxidase
UVB	=	Ultraviolet B
VRH	=	Verapamil
WHO	=	World Health Organization

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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