ISSN 2816-573X

REVIEW ARTICLE

Recent Advances of Carbon Dots for Treatment of Alzheimer's and Parkinson's Diseases

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Vedhanayagam M. Recent Advances of Carbon Dots for Treatment of Alzheimer's and Parkinson's Diseases. Int J Adv Nano Comput Anal. 2023;2(1):39-59.

Abstract

Neurodegenerative disease (ND) is an irreversible disease among the aged people in worldwide. ND is characterized by a progressive loss of neuron structure and function in the brain due to the formation of extracellular and intracellular misfolded or abnormal protein aggregates (β-amyloid, tau and (α-synuclein)). Numerous therapy strategies have been developed by many researchers to address this issue. However, the majority of the methods had only modest success in clinical studies. Transporting therapeutic molecules or drugs across the Blood- Brain Barrier (BBB) is a substantial problem for neurodegenerative disease diagnosis, targeting, and treatment. As a result, preparation of multifunctional material for simultaneously detecting and treating neurodegenerative diseases are high demand in the biomedical field. Carbon dots (CDs) have recently attracted interest for the diagnosis and treatment of neurodegenerative diseases due to easily crossing the blood-brain barrier, biocompatible, biodegradable, enhanced physico-chemical properties, provide tunable surface functionalization and optical properties, higher photostability, smaller size, non-invasiveness, facilitate targeted drug delivery and higher therapeutic efficacy. In this review work, we discussed the current progress of carbon dots in penetrating the blood brain barrier and their application in Alzheimer's and Parkinson's disease. Finally, the limitations and future prospects of carbon dots for neurodegenerative diseases are thoroughly examined.

Key Words: *Neurodegenerative diseases; Blood brain barrier; Carbon quantum dots; Graphene quantum dots; Drug delivery and bio-imaging*

Abbreviations

AD: Alzheimer Disease; PD: Parkinson Disease; BBB: Blood brain barrier; SNCA: α-Synuclein; PC12: Pheochromocytoma; GQDs: Graphene Quantum dots; Ct: Clitoria ternatea; *ς:* Zeta Potential; SH-SY5Y: Human neuroblastoma cells; IC-21: Mouse Macrophage cells; PC12: Rat pheochromocytoma cells; HeLa: Human cervical cancer cells; U-251: Human astrocytoma cells; SHG-44: Human Glioma cells; OPD: o-phenylenediamine ThT: Thioflavin T; hUCB – MSCs Human umbilical cord blood-derived mesenchymal stem cells; iNSCs: Induced neural stem cells; HUVECs: Human umbilical vein endothelial cells; SJGBM2: Pediatric Glioblastoma cell; HEK293: Human embryonic kidney cell.

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Received: June 06, 2023, Accepted: June 28, 2023, Published: July 11, 2023

Introduction

Neurodegenerative diseases (ND) have been receiving significant research interest in biomedical field because of its continuously growing incidence in aging populations [1-3]. The major reason for the formation of neurodegenerative diseases is accumulation of misfolded Prion like peptide/ proteins aggregation leads to an enhanced production of reactive oxygen species (ROS), neuroinflammation, gene mutation and cell death in central nervous system (CNS) [4-6]. Based on different protein aggregation and disease pathogenesis, ND has been classified into several types such as Alzheimer's disease (AD), Parkinson's disease (PD), Prion disease (PrD), Amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) etc [8]. Among them, Alzheimer's and Parkinson's diseases are the two most common neurodegenerative diseases which are characterized by degeneration of neurons in the hippocampus and substantia nigra respectively [9-10]. AD is distinguished by unusual accumulation of amyloid -β plaque (Aβ42) and neurofibrillary tau tangles, which cause brain damage and impair in language, memory, problem solving and other cognitive processes [11-13]. PD is differentiated by the aggregation of misfolded α-synuclein (α-syn) protein along with Lewy bodies (LB) in dopaminergic neurons, resulting in severe motor dysfunction such as slow movements, tremor, gait and balance disturbances etc [14-16]. These two neurodegenerative diseases share many clinical and pathological features due to formation of toxic amyloid -β plaque (Aβ42) and neurofibrillary tau tangles, and α-synuclein (α-syn) protein [17]. The exact pathogenic mechanisms for formation of toxic protein aggregates are still scanty due to multifactorial pathogenesis. However, some known connections indicating their role in dysregulation of cell signaling, oxidative stress, inflammation, apoptosis and other cellular abnormalities [18-20].

Based on the shared pathological features among these diseases, several therapeutic molecules or drugs (naturally derived plant products, proteins, peptides, siRNAs, and synthetic chemicals) have been developed by many researchers for the treatment of neurodegenerative diseases [21-29]. These therapeutic molecules or drugs were interacted with protein aggregated through electrostatic, hydrogen bonding (H-bonding), π-π stacking and hydrophobic interactions [30-33]. Most of the therapeutic molecules or drugs could not successful in clinical trials due to their inability to cross the blood-brain barrier (BBB), unfavorable biocompatibility and peripheral side effects etc [34]. The BBB is a well-ordered boundary between the central nervous system (CNS) and peripheral circulation that prevents most substances entering from blood to brain through circulatory system [35]. Therefore, developing an appropriate therapeutic molecules or drugs that can cross the BBB, as well as understanding their mode of transport is essential for the successful treatment of neurodegenerative disease.

In the past few years, delivering therapeutic molecule or drugs to central nervous systems with the aid of nanomaterial is attractive attention in neurodegenerative disease [36]. Because of their multifunctional properties such as smaller size (1-100 nm) with large surface area, easily crossing the blood-brain barrier, tunable surface functionalization and optical properties, higher photostability, simple synthetic methods, biocompatible, readily bind and disaggregate fibrils, targeted drug delivery and also simultaneously use as imaging probe and therapeutic material [37-39]. In this avenue, several nanoparticles such as metal/metal oxide, protein, polymeric and carbonaceous (Graphene oxide, Graphene, Carbon nanotube) have been used for treatment of various neurodegenerative diseases [39-45]. However, major challenges associated with most of nanoparticle are lower biodegradability, biocompatibility leads to accumulate in the brain and turn into toxic

substances, thus resulting in complications [40-46].

Hence, preparation of multifunctional nanomaterial with complete biodegradable nature is highly essential for successful treatment of neurodegenerative disease. Recently, Carbon dots (CDs) have been widely used in various biomedical applications (tissue engineering, drug delivery, bio-imaging, photothermal and photodynamic therapy) due to their unique optical properties, an enhanced biocompatibility and biodegradability [47-48]. The CDs also provided promising contribution in diagnosis, treatment and management of Alzheimer's and Parkinson's diseases (Figure 1). To the best of our knowledge, systematic review works on application of multifunctional carbon dots for simultaneously diagnosis and therapeutic treatment of neurodegenerative disease has not been reported so far. In this review, we discuss the recent advances of CDs in treatment of Alzheimer's and Parkinson's disease. Finally, limitation and future perspective of CDs for neurodegenerative diseases are discussed detailly.

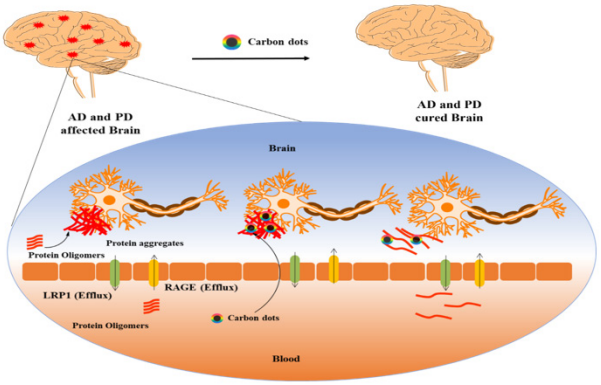

Figure 1) *Penetration of Carbon dots to BBB and destroy the amyloid plaques. After that the small amyloid plaques enter the blood stream via particular protein channels in the brain.*

Neurodegenerative Disease

Neurodegenerative disease is the progressive disease among the aged people. This diseased is associated with deterioration of neuron structure and function leads to neuronal death in different regions of the brain. Based on the type of misfolded protein such as amyloid-β, tau and α-synuclein, this disease has been categorized into Alzheimer's disease, Parkinson's disease, Prion disease, Amyotrophic lateral sclerosis and Huntington's disease etc. Among the various neurodegenerative diseases, AD and PD are most commonly found in aged people [49]. The key symptoms and different molecular mechanism of AD and PD are detailly discussed in the following sections.

Alzheimer's disease

Alzheimer's disease is one of most common neurodegenerative diseases that create the memory and learning dysfunction [50]. Even though, several research works carried out on this disease, the etiology and pathogenesis of the disease still unclear [50-52]. Currently, more than 50 million people are affected by Alzheimer disease in worldwide [53]. This disease is anticipated to become a major health issue with numerous socio-economic implications in future. Many research studies indicate that Alzheimer's disease (AD) is characterized by the coexistence of two hallmark pathways that lead to the functional loss of synapses and neurons: the accumulation and disposition of insoluble Aβ plaques and neurofibrillary tangles generated by the hyper-phosphorylation of tau proteins (P-tau), in addition to oxidative stress, cholinergic dysfunction, and inflammation [54].

The Aβ is formed from the amyloid- precursor protein (APP, also known as amyloid β A4 protein), which is broken by β-secretase and γ-secretase. Aβ monomer aggregates to form oligomers of varying molecular weight, which then aggregate to form fibrils of Aβ that further aggregate to form plaques in the brains of Alzheimer's disease patients [55]. Currently, nanoparticle-based approaches to treating Alzheimer's disease have mostly focused on interfering with Aβ aggregation or sequestering peptides in disaggregated form leads to preserve

the brain in normal condition. The nanoparticle-based approaches offer neuroprotection against oxidative stress and anti-amyloid therapeutics as well drug delivery beyond the BBB [56-58]. The following section describes the recently developed nanomaterials for treatment of AD disease.

Parkinson's disease

Parkinson disease is the second most neurodegenerative disease in central nervous system [59]. Currently, more than 10 million people are affected by the Parkinson disease mostly above age of 65 [60]. This disease shows various symptoms such as slow movement, tremor in hands and other joints, stiffness of limbs, difficulty in balance and coordination of various body parts and movements [61]. Several studies indicated that major pathological hallmark of PD is formation of misfolded α-Synuclein (α-Syn) protein aggregation, which is the primary constituent of Lewy's bodies [62-64]. This protein aggregation continuously destroys the significant neurons in the substantia nigra region resulting in death of neurons. These neuronal death decreases in the production of dopamine in brain [65]. Dopamine is the important chemical and widely used for instructing brain to carry out and control various task and motions. A reduction of dopamine level in brain leads to affect the movements and other physiological processes [66]. Mostly two strategies have been used to treat the Parkinson disease such as targeting α-synuclein accumulation and adding growth factors and other agents (including synthetic dopamine) [67-68]. Unfortunately, these treatments are only effective for modifying the symptoms of Parkinson's disease and not the underlying cause. Recently, the use of nanomaterials opens up exciting new possibilities for future therapies due to their unique physico-chemical properties and biocompatibility [69-70]. The following section describes the recently developed nanomaterials for treatment of PD disease.

Carbon Dots Synthesis and Optical Properties

Carbon dots (CDs) are new type of fluorescent carbon nanomaterials with diameter around 1-10 nm. Generally, CD contains carbon based sp^2/sp^3 skeleton structure with higher oxygen containing groups on the surface [71]. In 2004, carbon dots were unintentionally found by Xu et al during the electrophoretic purification of single-walled carbon nanotubes [72]. The carbon dots are classified into several types based internal chemical structure and functional groups present on the surface such as Graphene quantum dots (GQDs), Carbon polymer dots (CPDs) and Carbon quantum dots (CQDs) [73]. The carbon dots were synthesized from various natural and synthetic carbon sources through using top-down and bottom-up methods (Figure 2) [74-75]. In top-down methods, large size of precursor materials is converted into the smaller size of nanomateirals.

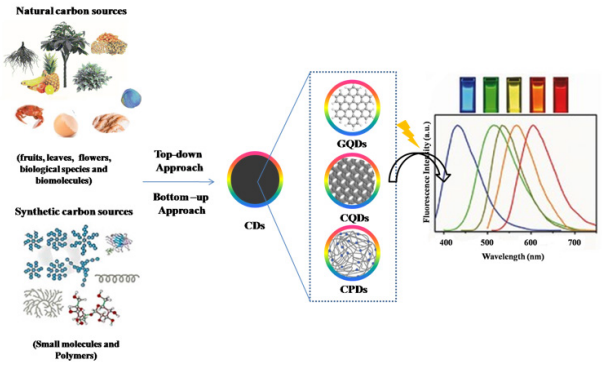

Figure 2) *Synthesis of different types of carbon dots (graphene quantum dots (GQDs), carbon quantum dots (CQDs), carbon polymer dots (CPDs)) and their optical properties. Reproduced with permission [74-75]. Copyright 2017 and 2014, The Royal Society of Chemistry.*

Researchers have been reported that various top-down methods have been involved in preparation of CDs such as Arc discharge deposition, Laser ablation, electrochemical synthesis, Ultrasonication [76-77]. In bottom-up methods involve building up of smaller molecule into nanometer size. Several bottom methods have been employed for preparation carbon dots including hydrothermal,

microwave, solvothermal, reverse micelles and pyrolysis methods [78-79]. Each synthetic method has both advantages and disadvantages in enhancing the quantum yields of carbon dots. For examples, carbon dots prepared from top-down approach provides higher quantum yield, better surface property but it's required higher time, expensive chemical and instruments. Particularly, fabrication of large quantity of fluorescent carbon dots from greener route has been showing facile and eco-friendly approaches. In these methods, various plant materials, biological species, biomolecules have been used as starting materials for preparation of carbon dot.

For example, Achyut et al have prepared carbon quantum dots from natural source tea powder through thermal treatment process (200^{o}C for 8 h) [80]. The obtained carbon quantum dots exhibited around 2.7 nm size (zeta potential: -229mV) with blue color photo emission (468 nm-554 nm). Similarly, Gayathri et al have used maple tree leaves for the synthesize of blue-emitting carbon quantum dots (size 1-10 nm) through hydrothermal method for selective detection of Cesium [81]. In addition to this, Prathik et al. have used hydrothermal process (300^{o}C for 8 hours) to prepare graphene quantum dots (N-GQDs and F-GQDs) from plant leaf extracts of Neem (*Azadirachta indica*) and Fenugreek (*Trigonella foenum-graecum*) [82]. Two synthetic graphene quantum dots had sizes of 5 nm and 7 nm and quantum yields of 41.2% and 38.9%, respectively. Finally, this graphene quantum dots were used for white LEDs applications. Xi et al. used a hydrothermal technique to prepared fluorescent carbon quantum dots from cynobacteria for bioimaging application [83]. The synthesized carbon dots demonstrated higher monodispersity (size 2.48 nm), biocompatibility, photostability and excitation dependent emission performance. Zehui and co-worker were synthesized carbon dots (size 2.1 nm) from egg white via one step hydrothermal method [84]. The synthesized carbon shows blue color photo emission with 64% quantum yield. This carbon dots were used for bioimaging and sensor (detection of Fe^{3+} ion) applications. Similarly, Bovine serum albumin (BSA) is also used as precursor for synthesis of nitrogen doped carbon dots (NCDs) by simple, convenient and one-step hydrothermal method. The obtained blue emission carbon dots (size 4 nm) exhibited higher photo stability and 44% of quantum yield [85].

Carbons dots have been widely used as bio-imaging probe to visualize the cells/ tissue in various biomedical applications due to their exceptional photoluminescence property. The smaller size of carbon dot was absorbing the UV- light in the range 270 nm -320 nm due to the presence of π-π* and n-π* electronic transition. The former electronic transition corresponds to -C=C- conjugated systems, whereas the later one ascribed to hetero atom in the functional groups (oxygen and nitrogen etc). These carbon dots show excellent optical properties such as excitation dependent emission, solid-state fluorescence, phosphorescence, up-conversion photoluminescence and piezo-chromic fluorescence because of their surface functional groups, surface defects and surface edge effects. In addition to this, the carbon dots exhibit fluorescence signal in the near infrared region when introducing or doping hetero atom in the CDs [86].

The surface defect in carbon dots offer either radiative or nonradiative recombination centers of excited electrons and holes, which highly affects the photoluminescence properties of carbon dots [87]. It has been observed that the fluorescence peak was shifted to longer region (red-shift) by introducing or doping several functional groups such as epoxy, hydroxy, nitrogen and phosphorus containing molecules [88-89]. Carbon dots are showing better photocatalytic behaviours because of their electron donor and acceptor nature [90]. When CDs are exposed to light, electrons and

holes are created and easily transported to target molecules, causing the photoluminescence of carbon dots to decay by electron donor or acceptor mechanisms [91]. Subsequently, carbon dots have been used as imaging probes to detect various biomolecules, allowing target analytes to be recognized at very low levels [92]. Recently, carbon dots and functionalized carbon dots are widely used in various applications such as optoelectronic devices, catalysis, sensing and bio-imaging and drug delivery due to their simple synthetic routes, smaller size with excellent optical properties [93].

Blood-Brain Barrier Penetration of CDs

Human brain and spinal cord of the central nervous system (CNS) are strongly protected by a unique barrier called blood-brain barrier (BBB). This BBB is a complex multicellular structural barrier in the CNS that consists of a highly semipermeable membrane of endothelial cells, which are directly interconnected by tight intracellular junctions. These endothelial cells with tight junctions are allowing only O_2, CO_2, water, soluble compounds in fat, nutrients and small molecules (glucose, amino acids) to pass while preventing pathogens and most macromolecules from entering the CNS [94]. Transporting the suitable drug or therapeutic molecules across the BBB is primary factor in neurodegenerative diseases.

The mechanism for penetrate the BBB can be classified as passive and active routes [95-96]. Passive diffusion allows small and lipophilic molecules to cross the BBB. Large, hydrophilic and highly charged molecules are usually transported through active routes such as receptor- and adsorption-mediated endocytosis and carrier mediated penetration [97]. Several neurodegenerative diseases have no proper treatment due to the blood-brain barrier hinders the transport of drugs from blood stream to the brain. Hence the developments of multifunctional nanomaterials for transporting drugs or therapeutic molecules across the blood brain barrier are essential for treatment of ND. Numerous research studies indicate that use of CDs or surface functionalized CD as ideal nanocarriers for the treatment of several neurodegenerative diseases because of their higher penetrating ability via BBB for delivery of appropriate quantity of drug at target brain aggregates [98-100].

Seven et al have prepared carbon dots (GluCDs) from D-glucose precursor through hydrothermal method (Figure 3) [101]. The prepared luminescent carbon dots were covalently conjugated with fluorescein dye and then injected into the heart and tail of zebrafish and rat models respectively. Confocal and histopathological analysis display that carbon dots were accumulated in the neurons of CNS and implying that GluCDs can cross the BBB of both vertebrate species. In addition to this, GluCDs also carry the fluorescein dye molecules into the CNS. It has been reported that surface functionalization of carbon dots also facilitate the BBB crossing ability in various animal model [102-104]. For example, Li et al have reported that transferrin conjugated CDs (Size: 5 nm) can easily enter into the CNS than CDs alone [105].

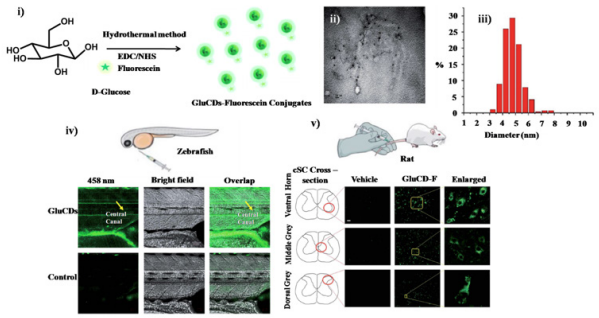

Figure 3) *a) Schematic representation of Fluorescein –GluCDs from D-glucose by hydrothermal method, b and c) HR-TEM and Histogram image of GluCDs, d) Confocal image of GluCDs-Fluorescein injected zebrafish, Accumulation of GluCDs-Fluorescein in the CNS of zebrafish (Yellow color arrow mark indicate the central canal of spinal cord of zebrafish, Scale bar: 20 nm). E) Accumulation of GluCDs-Fluorescein in different parts such as ventral horn, middle grey and dorsal horn of rat CNS and their corresponding spinal cord cross-section camera obscura schematic indicating the area of the image taken are displayed at the left column. (Scale bar: 50 mm). Reproduced with permission [101]. Copyright 2021, The Royal Society of Chemistry (RSC).*

In that, transferrin labeled with fluorescent dye was covalently conjugated with CD and then conjugates were intravascularly injected into the heart of the zebrafish to study their efficiency to penetrate the central nervous system. The bright fluorescence signals were observed in the CNS of zebrafish. This observation clearly suggested that transferrin labeled fluorescent dye conjugated CDs were highly cross the blood-brain barrier via transferrine receptor-mediated endocytosis. Similarly, Mintz et al have demonstrated that tryptophan carbon dots were easily cross the blood-brain barrier of zebrafish via LAT1 transporter-mediated endocytosis [106].

Yan and his coworker have observed that glycosylated carbon dot integrated with Epigallocatechin -3-gallate (gCDs-E) were effectively cross the blood brain barrier in mice model. Zhou et al have demonstrated that smaller size of amphiphilic yellow- emissive CDs (with or without coating) were easily crossed the blood-brain barrier of zebrafish model through passive diffusion [107]. In that study, stronger fluorescence signals were observed in the central canal of spinal cord when exciting at 405 nm due to the uniform distribution of amphiphilic nature CDs in central canal of spinal cord. These results suggested that CD and surface functionalized CDs are potential drug delivery and a bio-imaging material leads to useful for various central nervous diseases.

Application Carbon Dots in AD and PD

Recently carbon dots used as multifunctional drug, drug carrier as well as imaging agent in Alzheimer's and Parkinson's diseases due to their higher penetration ability across the blood-brain barrier, tunable surface functionalization, unique optical property, biocompatibility, higher drug loading capacity and release sufficient amount of drug at targeted protein aggregates [108-109]. Carbon dots preparation, optical properties, blood brain barrier penetration and their application in Alzheimer's and Parkinson diseases are detailly given in (Table 1). Several research studies have demonstrated that CDs and surface functionalized CDs were highly prevent the formation of protein aggregates and also change the protein misfolding pathways in central nervous system [110]. For instance, Liu and his coworker have reported that GQDs were significantly inhibit the $A\beta_{1-42}$ peptide aggregation as well as reduce the toxicity associated with $A\beta_{1-42}$ peptide in central nervous system [111]. This observation can be attributed to the strong electrostatic interactions between the GQDs and $A\beta_{1-42}$ peptide.

Similarly, Li et al have found that the β-sheet structure of Aβ peptides was converted into the random coils or amorphous aggregates when smaller size of CQDs (size 2-4 nm) were introduced during the aggregation of Aβ fibrils [112]. Generally, the hydrolytic decomposition of acetylcholine (ACh) in the central nervous system by Acetylcholinesterase (AChE) can accelerate the assembly of amyloid peptides into amyloid fibrils, and this process plays an important role in the development of Alzheimer's disease (AD) [113]. As a result, an effective strategy in current AD treatment is to inhibit the increase in ACh level caused by AChE. Recently, Qian et al have developed carbon quantum dots based fluorescent assay for quantitatively detect and inhibit the Acetylcholinesterase (AChE) activity by using acetylthiocholine (ATCh) and Cu (II) ions [114].

In this method, fluorescence property of CQDs was quenched in the presence of Cu (II) ions due to the interaction between the carboxyl groups of CQDs and Cu (II) ions leads to form a CQDs-Cu(II) aggregates. After simultaneous addition of ATCh and AChE into the CQDs-Cu (II) aggregated system, the ATCh was hydrolysed into the thiocholine by the catalytic reaction of AChE. Subsequently, the produced thiocholine was strongly binded with Cu (II) ions from CQDs-Cu (II) aggregates leads to recover the

TABLE 1

Summarization of Carbon dots synthesis, characteristics and their application in Alzheimer's and Parkinson's diseases

Type of Carbon dots used for ND	Synthesis method	Coated Drugs/ genes/peptides/small molecules	Physico-chemical and Optical properties	In vitro Cell lines	In vivo model	Salient Features	Applications	References
GQDs	Microwave	-	Sphere shape with, size 4.0 ± 0.7 nm	SH-SY5Y	-	Structural changes of β-amyloid peptide ($A\beta_{1-42}$) aggregation	Alzheimer's Diseases	[111]
CQDs	Pulsed Laser Ablation	-	Size 2 - 4 nm	SH – SY5Y	Transgenic strain C.elegans CL2006	Highly reduce the Aβ42 deposition and cytotoxicity Enhance the biological activity of AD model C elegans GL2006	Alzheimer's Diseases	[112]
CQDs	Chemical Oxidation	-	Size 2-5 nm	-	-	Detection and inhibition of acetylcholinesterase (AChE)	Alzheimer's Diseases	[114]
GS and GQDs	Pyrolysis		GO diameter: 314 ± 50 nm (ς = -38mV) GQDs size: 65 ± 10 nm (ς = -8 mV)			Inhibit the α -synuclein amyloid formation	Parkinson's Diseases	[115]
GQDs		-	Thickness ± 1.74 nm	SH-SY5Y	mice	Inhibit the fibrillization of α -synuclein and dis-aggregate the mature fibrils. Penetrate the BBB	Parkinson's Diseases	[116]
CF-GQDs and C-GQDs	Pyrolysis and thermo-oxidative cutting	-	Spherical shape (3.02 ± 0.913 – 3.69 ± 0.98 nm)	hUCB-MSCs, HUVECs, iNSCs	-	Inhibited α-syn fibrillation and protect the neurons against cellular damage	Parkinson's Diseases	[117]

CDs	Hydrother-mal	L-Lys or D-Lys	Spherical shape with 3.9 ± 1.1 nm, Zeta potential –2 ± 1- 5.9 ± 0.4	SH-SY5Y	-	Alter the amyloid β 42 aggre-gation and cytotox-icity	Alzhei-mer's Diseases	[118]
GQDs	Hydrother-mal	Glycine –Pro-line-Gluta-mate	Spherical shape with Particle size ~ 18 nm	-	APP/ PS1 trans-genic mice	Inhibit the aggrega-tion of Aβ1-42 fibrils and enhance the learn-ing and memory ability	Alzhei-mer's Diseases	[119]
CDs	Ultrasoni-cation	3-ami-no-1-pro-panol and Dietha-nolamine (DEA)	Spherical shape with size 3.4 ± 1.0 nm, Zeta Potential (-15.3 mV) Yellow color with amphiphil-ic nature	SJGBM2 and HEK293	zebrafish	Cross the BBB, Inhibit overepres-sion of the amyloid precursor protein (APP) and β-amyloid	Alzhei-mer's Diseases	[107]
Ct-GQDs	Microwave	*Ct*	Spherical shape with size 10 ± 1.3 nm (ς = -46 ± 0.4 mV) Higher stability Surface area 412 m^2/g		Wistar Rats	Inhibition of acetyl cholin-esterase enzyme Increase the level of gluta-thione and protein and decrease the lipid peroxide and nitric oxide Cross BBB Reduce the Alzheimer like symp-toms	Alzhei-mer's Diseases	[121]
CQDs	Hydrother-mal	Na-citrate	Size 2 -4.2 nm Low cytotox-icity	SH-SY5Y		Disag-gregation of mature HEWL fibrils	Alzhei-mer's and Parkin-son's Diseases	[122]

gCDs-E	Solvothermal	Glycosyl, Epigallocatechin -3-gallate	Circular or oval shape, particle size 25.5 nm. Quantum yield 9.8%	SK-N-SH	Transgenic mice model	Prevent the misfolding of Aβ and inhibit its aggregation, Reduce Aβ mediated cytotoxicity Inhibit the activity of *Candida albicans* BBB penetration, Cleaned Aβ deposition and enhanced memory impairment Biocompatible	Alzheimer's Diseases	[99]
OPCDs	Hydrothermal	o-phenylenediamine	Spherical shape, Particle size ~7.3 nm, Zeta Potential ~ 17.4 mV	PC12	-	Better cell viability, Inhibiting Aβ and Aβ-Cu (II) complex based aggregation,	Alzheimer's Diseases	[123]
CDs-EDA and CDs-Urea	Hydrothermal	Tryptophan	Higher photoluminescence (QY =48% and 21.5 ± 3.2%), Lower toxicity, Size 4.1 and 6.2 nm, Spherical Shape,, Zeta potential = -9.02 ± 0.17 and -10.8 ± 0.54 mV	SJGBM2 and CHLA266	Zebrafish	Cross the BBB	Alzheimer's Diseases	[106]
Dopamine @ CS-CDs	Pyrolysis	Dopamine	Spherical shape with size 3 nm Higher biocompatibility	IC-21 and SH-SY5Y		Drug loading efficiency (80%) Tracing the drug delivery via bioimaging	Parkinson's Diseases	[124]

quenched fluorescence of CQDs (~70%) due to the re-dispersion of CQDs. Notably, the ATCh activity was directly correlated with fluorescence intensity of CQDs.

It has been reported that morphology of carbon nanomaterials also affects the protein aggregation in neurodegenerative diseases. For example, Ghaeidamini et al. have investigated an influence of different morphology carbon nanomaterial (GO sheet and GQDs) on fibril formation of α-syncline protein (Figure 4) [115]. Both carbon nanomaterials were significantly inhibiting the α-syncline fibril formation in concentration dependent manner by two different mechanisms.

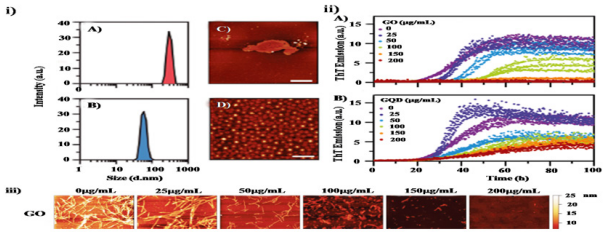

Figure 4) *Hydrodynamic size of carbon nanomateirals was analyzed through DLS analysis a) GO sheets b) GQDs; Morphology of carbon nanomateirals was characterized by using AFM analysis c) GO sheets and d) GQDs (All the scale bare are 1mm). ii) Fibril formation of a-Synuclein (50mM) in the presence of a) GO sheets and b) GQDs at pH 7.4 and 37 oC (25 mM Tris-HCl buffer with 150 mM NaCl) was observed by ThT- fluorescence (n=3). iii) Morphology of fibrils in the presence of different concentration of GO sheets and CQDs were analysed in the AFM analysis (scale bare 2 mm). Reproduced with permission [115]. Copyright 2020, The Royal Society of Chemistry (RSC).*

The GO sheets were interacting with both monomers and fibrils of α-syncline protein, whereas GQDs were only interact with fibers of α-syncline protein. Among the two-carbon nanomaterial, GO sheets were greater binding affinity along with completely inhibiting the fibril formation process of α-syncline protein than GQDs due to their higher negative charge on surface resulting in more adsorption of positively charge monomers and fibril through electrostatic interactions. This observation suggested that morphology and physiochemical properties of carbon nanomaterial strongly affect the fibril formation process of α-syncline protein. Kim et al have reported that GQDs were effectively penetrate the BBB and protected the neuronal death, synaptic loss in Parkinson disease via inhibiting fibrillization of α-synuclein and dis-aggregate the matured fibrils [116].

The GQDs were interacted with α-Syn through electrostatic interactions and fibrils was dissociated by hydrophobic interactions leads to secondary structure was changed. In that study they found that the secondary structure of β-sheet component of α-synuclein was decreases from 53.3 ± 3.5% to 29.8 ± 3.4% and increase the α-helix / random coil from 4.2 ± 1.2% to 19.8 ± 1.5% and 20.1 ± 5.7% to 24.6 ± 3.6% respectively.

Kim et al have prepared luminescent GQDs from various country coffee beans (Ethiopia, Mandheling and Kenya AA) through pyrolysis and thermal oxidative cutting methods (Figure 5) [117]. The prepared ultra smaller size of luminescent GQDs were added in α-syn preformed fibils (α-syn PFFs) induce accelerated α-syn fibrillation process (sporadic *in vitro* model) and subsequent changes were monitored through Alamar Blue, Immunostained neurons assays and observed results were compared with carbon fiber derived GQDs. The results indicated that coffee bean-derived GQDs were effectively inhibit the unusual α-synuclein fibrillation and the protect the neurons from related subcellular damages.

Malishev et al. have synthesized ~4 nm size of enantiomeric carbon dots (D and L -Lys-C-dots) from D-lysine and L-lysine based carbon precursor via hydrothermal method (Figure 6) [118]. The prepared carbon dots were treated with $A\beta_{42}$ peptide for 24 h and subsequent structural changes, fibrils morphology and cytotoxicity were studied through CD, Cryo-TEM microscope and cell viability assay. In CD

spectrum, $A\beta_{42}$ peptide in buffer shows a typical peaks at 195 nm and 218 nm due to the structural transformation of $A\beta_{42}$ peptide from random coil (t =0) to β-sheet structure (t =24 h). This structural transformation was not altered when $A\beta_{42}$ peptide was treated with D-Lys-C-dots. In the case of L-Lys-C-dots treated $A\beta_{42}$ peptide sample, random coil to β -sheet transformation of $A\beta_{42}$ was significantly inhibited in the CD spectrum. This observation was consistent with Cryo-TEM analysis. As can be seen in Figure, the high density of longer linear fibrils were observed in D-Lys-C-dots treated $A\beta_{42}$ peptide, whereas few short linear fibrils along with nanoparticle were directly adsorbed on the surface of fibril was observed in L-Lys-C-dots treated $A\beta_{42}$ peptide sample. Furthermore, L-Lys-C-dots treated $A\beta_{42}$ peptide exhibited higher cell viability compared to D-Lys-C-dots treated $A\beta_{42}$ peptide.

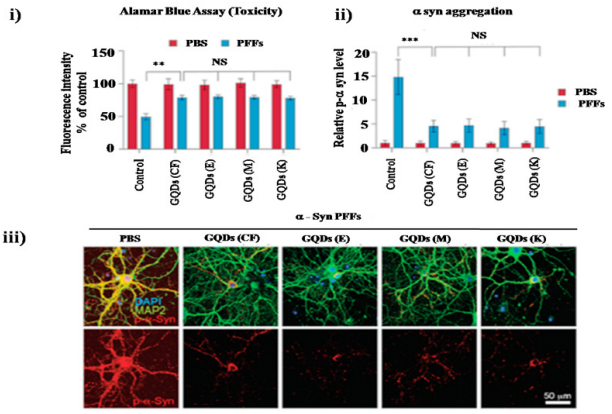

Figure 5) *The influence of coffee bean – derived GQDs on a-syn PFFs –induced primary neuronal toxicity and a-syn pathology. i) The mouse cortical neurons were treated with a-syn PFFs, carbon fiber derived GQDs(CF) and coffee-bean derived GQDs (E: Ethiopia, M: Mandheling and Kenya AA, Concentration- 5mg/mL, n=6 each group). Neuronal toxicities were analyzed through Alamar Blue Assay after treatment of 7 days. ii and iii) Representative p-a-syn immunostained neurons at 7 days after treatment with p- a-syn antibody. The p-a-syn immunofluorescence intensities were assessed and normalized to the PBS control (n=6, group). Significant levels are analysed through ANOVA software with Tukey's multiple comparison test and obtained results are indicated as asterisks: **p<0.01, **p<0.001. Reproduced with permission [114]. Copy Right (2021) Multidisciplinary Digital Publishing Institute (MDPI).*

These obtained results can be attributed to rapid adsorption of L-Lys-C-dots on $A\beta_{42}$ fibril structure which result in changing the secondary structure, fibril morphology and cytotoxicity.

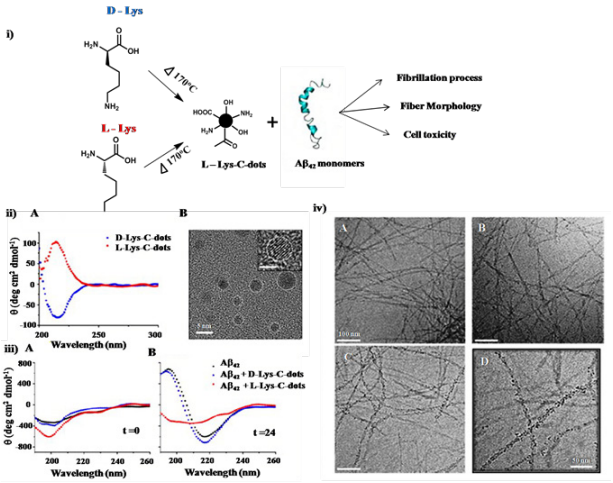

Figure 6) *Schematic representation of synthesis of enantiomeric carbon dots from D or L-lysine carbon source, ii) Characterization of enantiomeric carbon dots A) CD spectrum of D-lysine C-dots and L-lysine C-dots, B) HR-TEM image of L-lysine C-dots (inset image: lattice fringes of C-dots, Scale bar: 2 nm), iii) Secondary structure of Ab42 peptide in the presence and absence of D-lysine C-dots and L –lysine C-dots A) CD spectra recorded at t=0, B) CD spectra recorded after 24 h, iv) Morphology of Ab42 fibril in the presence of A) Buffer alone B) buffer + D-Lys C-dots, C-D) buffer + L-Lys C dots after 24h incubation. Scale bars: 100 nm (A-C) and 50 nm (D). Reproduced with permission [115]. Copyright 2018, The Royal Society of Chemistry (RSC).*

Xiao and his coworkers have developed glycine-proline-glutamate conjugated graphene quantum dots (GQDG) based nano drug carrier for treatment Alzheimer's disease [119]. In this study, the prepared nano drug carrier was improved the learning and memory ability of APP/PSI mice via prevents the aggregation of $A\beta_{1-42}$ fibrils and reduces the inflammatory response. Zhou et al have used citric acid and o-phenylenediamine as a precursor for preparation of 3 nm size of amphiphilic yellow-emissive CDs through ultrasonication method. The prepared CDs were effectively crossing the blood brain barrier as well as significantly inhibiting the formation of amyloid precursor protein (APP) and Aβ plaques (Aβ).

This observation can be attributed to the hydrophilic functional group could be useful for inhibit the formation of Aβ plaques, whereas hydrophobic functional could be beneficial for cross the BBB via passive diffusion. This result indicated that amphiphilic nature of CDs were

potential material for treatment of Alzheimer's related disease. It has been documented that *Clitoria ternatea (ct)* exhibit better memory enhancement effects because of their histidine and threonine components in chemical structure [120]. Tak et al have prepared stable graphene quantum dots (ctGQDs, size 10-20 nm) from flower extract of *Clitoria ternatea* via one-pot microwave assisted method [121]. The smaller size of ctGQDs exhibited higher inhibition of acetyl cholinesterase enzyme (86.32 ± 1.52%), enhance the level of glutathione and protein as well as reduce the level of lipid peroxide and nitric oxide. This observation indicated that smaller size of ctGQDs were easily crossed the blood-brain barrier leads to effective in decreasing the Alzheimer-like symptoms in rodent model due to the synergic effect of Clitoria ternatea and GQDs. Guerrero et al have synthesized spherical shape of sodium-citrate derived CQDs through one-spot hydrothermal method (Figure 7) [122].

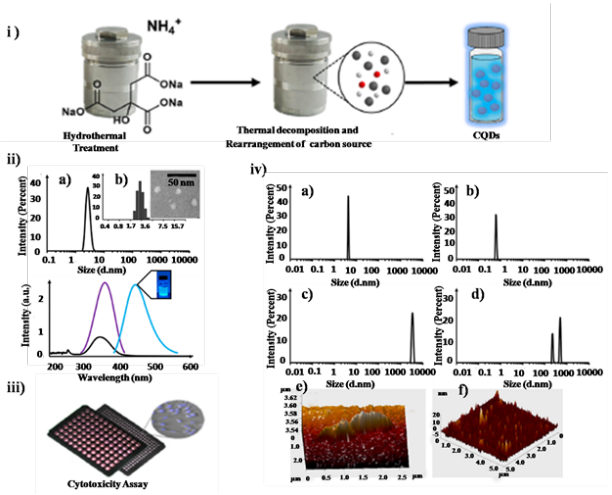

Figure 7) *i) Synthesis of CQDs from organic precursor through hydrothermal method, ii) Characterization of CQDs a) Hydrodynamic size and b) morphology, iii) Cytotoxicity assay of synthesized CQDs (Human Neuroblastoma cells), and iv) Dynamic light scattering data of a) HEWL oligomers b) Na-citrate CQDs treated HEWL (conversion of oligomers to monomers) c) mature HEWL fibrils d) Na-citrate CQDs treated with mature HEWL fibrils (conversion of mature fibrils into smaller aggregates) e) AFM image of HEWL fibrils and f) AFM image of HEWL in the presence of Na-citrate CQDs. Reproduced with permission [119]. Copyright 2021, American chemical Society (ACS).*

The smaller size with spherical shape of CQDs were rapidly destructing the fibril formation process of amyloid protein (Hen-Egg White Lysozyme as a model protein) due to their greater binding affinity with fibril via several interaction mechanism such as π-π stacking, non-covalent and hydrophobic interactions. Yan et al have prepared 25.5 nm sizes of glycosylated carbon dots (gCDs) from glucose by a solvothermal method. The prepared gCDs was coated with Epigallocatechin-3-gallate (EGCG or E) via non-covalent interactions. Subsequently, they evaluated the efficiency of gCDs-E in preventing Aβ fibrillization and disaggregating fibrils. The obtained result indicated that gCDs-E significantly inhibit and disaggregate the Aβ fibrils (average length -648 nm) into small fragments (average length -3.6 nm) after 24h. This observation was further confirmed with CD spectra, the β- sheet structure of Aβ peptide completely changed to random coil structure in the presence of gCDs-E after 24 h. The secondary structure analysis indicated that β- sheet component of Aβ peptide decreases from 55.7% to 31.2% as well as increases the random coil components from 19.3% to 35.9%.

The inhibition process was quantified through Thioflavin T (ThT) assay. In the absence of gCDs, Aβ peptide showed stronger fluorescence intensity, whereas in the presence of gCDs and gCDs-E the fluorescence intensity was highly reduced and inhibition efficiency was 62.97% and 90% respectively. In addition to this, gCDs-E shows biocompatible, better antifungal functions against *Candida albicans*, reduce the toxicity of Aβ peptides, highly penetrate the blood-brain barrier and enhance the memory deficits of APP/PS1 mice. These observations imply that gCDs-E could be use as potential therapeutic materials for treatment of Alzheimer's disease. Similarly, Chung et al have used o-phenylenediamine (OPD) as a precursor for multifunctional luminescent carbon dots (OPCDs) preparation through hydrothermal method [123]. The prepared OPCDs was inhibit the Cu(II)-mediated Aβ aggregation due to

presence of nitrogen containing polyaromatic functional groups on surface of OPCDs were easily attract the Cu(II) resulting in altered the secondary structure of Aβ peptides. In addition, upon light irradiation, the photo- excited carbon dots oxidize Aβ peptides lead to disrupting the Cu (II)-mediated Aβ aggregation.

This observation suggested that OPCDs shows potential therapeutic materials against Cu (II)-mediated Aβ aggregation in Alzheimer's disease due to their synergistic effect such as chelating Cu(II) and inhibiting Aβ aggregation. Mintz et al have reported that CDs-EDA- tryptophan shows higher ability to cross the blood-brain barrier in central nervous system of zebrafish due to the presence of tryptophan molecule on surface of CDs leads to potential materials for Alzheimer's disease. Mathew et al have prepared ~144 nm size of luminescent nano-drug carrier materials by integrating chitosan coated carbon quantum dots with dopamine (dopamine@CS/CD) [124]. The prepared dopamine@CS/CD material exhibited higher drug encapsulation efficiency (80%), better biocompatibility against SH-SY5Y and IG-21 cell lines (97%), sustained dopamine release towards neurodegenerative diseases as well as tracking the drug delivery process via bioimaging. This observed result can be attributed to the presence of CQDs in luminescent nano-drug carrier materials.

All the results suggested that CDs and surface functionalized CDs were easily penetrate blood-brain barrier and deliver the neuroprotective peptides in CNS, inhibit the formation of protein aggregates, reduce the protein aggregate induced toxicity and inflammation, facilitate the detection of protein aggregation as well as monitoring of treatment process (non-invasive imaging) leads to use as potential materials for neurodegenerative diseases.

Conclusion

A broad literature review suggested that the treatment of AD and PD related neurodegenerative diseases have be significantly improved by using smaller size of multifunctional carbon dots with advanced technology. Smaller size of multifunctional carbon dots can easily cross the blood brain barrier, capability to rapidly bind and disaggregate fibrils, decrease invasiveness, multiple drug load efficiency and release in target and sustained manner, biocompatible, inhibit the disease associated enzymes, protect the neural cells, simultaneously use as drug and imaging probe during the real time in-vitro and in-vivo analysis. In the near future, the combination of multifunctional carbon dots with precise strategy and advanced technologies will undoubtedly result in a promising diagnostic and therapeutic tool to treat Alzheimer's and Parkinson's disease.

Although several research works focused on the application of multifunctional carbon dots on neurodegenerative diseases, there is still have many limitations and unsolved challenges that should be addressed before using carbon dots in clinical applications. The following are some of the factors that should be taken into account further.

- Currently, all the available treatments are temporary improvement in brain functions but there is no proper curable treatment for neurodegenerative diseases. So, the understanding the origin of biological process and pathogenesis behind the formation of neuronal degeneration or directly targeting the neuronal degeneration could provide a suitable cure for neurodegenerative disease.

- The influence of carbon dots on protein aggregations are highly depends on the size, shape, charge and chemical composition. Several *in-vitro* and *in-vivo* studies are essential to identify how nanoparticle behaves on protein aggregations under different combinations of these factors.

- Various synthetic methods, size and surface functionalization or coating offer lower cytotoxicity in synthesized carbon dots. So, further research is needed to evaluate about the lower cytotoxicity of carbon dots before the clinical trials.
- Understanding the carbon dots structure, function and cellular toxicity is highly essential for application of carbon dots for neurodegenerative diseases. Because some carbon dots can create the side effect on targeting sites and other organs in central nervous system. Preparation of suitable carbon dots is compatible with neuronal tissue and without side effect after treatment is necessary to minimize the clinical trials.
- Design and developing single multifunctional carbon dots for various neurodegenerative diseases is significant challenging in this field. Because of up to now a very limited genetic proof has been identified for the association between these neurodegenerative diseases. To mitigate this problem, more number of studies needs to be carried out to understand the common molecular mechanism which is connecting the neurodegenerative diseases.

We anticipate that continued research with multifunctional carbon dots for neurodegenerative diseases over the next several years will advance the field of neural tissue regeneration by focusing on overcoming multifunctional carbon dots limitations.

Authors Contributions

M.V. developed an idea and constructs the entire manuscript. Author M.V. have given approval to the final version of the manuscript.

Acknowledgment

Author M.V. would like to thank Department of Science and Technology, Government of India for financial support (DST-INSPIRE Faculty Fellowship, Ref. No. DST/INSPIRE/04/2022/02114 and Faculty Registration No. IFA22-CH 379).

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