Dual-targeted carbon-dot-drugs nanoassemblies for modulating Alzheimer's related amyloid-β aggregation and inhibiting fungal infection

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Keywords:
Glycosylated carbon dots
Epigallocatechin-3-gallate
Amyloid-β peptide
Candida albicans
Alzheimer’s disease

ABSTRACT
Amyloid aggregation and fungal infection, especially amyloid beta (Aβ) peptide and Candida albicans are considered as two of the crucial pathogenic agents in Alzheimer’s disease (AD). In this work, we propose an innovative treatment strategy for AD, targeting at not only Aβ aggregation but also Candida albicans infection. Here, a high-performance nanomaterial, namely gCDs-E, have been prepared by self-assembled of glycosylated carbon dots (gCDs) and epigallocatechin-3-gallate (EGCG). Surprisingly, gCDs-E can not only suppress the fibrillation of Aβ and disaggregate Aβ fibrils, but also effectively inhibit the activity of Candida albicans. More importantly, the prepared gCDs-E can effectively cut down the cytotoxicity of amyloid aggregations, and the cell viability reached to 99.2%. In addition, the capability of the gCDs-E for blood brain barrier (BBB) penetration was observed using a normal mice model. Above all, the gCDs-E greatly cleaned Aβ deposition and improved memory impairment in APP/PS1 transgenic AD model mice, confirming its potential as therapeutic agent for AD treatment.

1. Introduction
Alzheimer’s disease (AD), also namely dementia, is the most prevalent form of neurodegenerative disorder [1–3]. Although the pathogenesis of AD has not been clearly and thoroughly confirmed, its emphatic pathological traits have been verified, which is the extracellular deposits of amyloid aggregation from the amyloid-β peptides (Aβ) [4–10]. The therapeutic and preventive methods of AD including inhibiting the aggregation of Aβ into fibrils and oligomers is also effectual and widely accepted [11–17]. However, the recent failure of clinical trials suggests that further efforts on AD research is still demanding [12]. Interestingly, recent intense research indicates that some pathogenic microorganisms exist in the brain and postulated to be involved with Aβ or even to AD [18–22]. For example, Pisa et al. [18] directly visualized fungal components inside neurons from AD patients. Wu et al. [20] showed that Candida albicans can cross the BBB and cause a highly localized cerebritis. Moreover, Aβ accumulates within the activated microglial and astroglia cells, which are induced by Candida albicans. These evidences even indicated that Aβ peptides enhanced both phagocytic and antifungal activity from cells. According to Wu’s research [20], Candida albicans can cause a highly localized cerebritis marked by the accumulation of activated microglial and astroglial cells around yeast aggregates, forming fungal-induced glial granulomas. In addition, they found that large amounts of Aβ peptides and insoluble Aβ aggregation accumulated around the yeast cells. This related research indicates that the more serious the fungal infection, the more obvious amyloid fibrillation.

Currently, most of Aβ inhibitors including biomolecules [23–26], functionalized nanomaterials and nanoparticles [16,17,27–31], have been shown to decelerate the aggregation of Aβ and suppress cellular toxicity of amyloid. For example, Sun et al. [32] reported a mesoporous...
Glycosylated carbon dots (gCDs) were firstly prepared using glucose as a precursor by a solvothermal method. Following, gCDs-E was assembled from EGCG and gCDs through hydrogen bonding, π–π stacking interaction and electrostatic binding [54]. The morphology and particle size of gCDs and gCDs-E were characterized by transmission electron microscopy (TEM) and atomic force microscopy (AFM). As shown in Fig. 1a, gCDs exhibit a uniform dispersion without any apparent aggregation, and the average size is about 4.25 nm. AFM image (Fig. S1) reveals that gCDs disperse nicely with a particle’s height about 1.5 nm. The size distribution of both TEM and AFM indicate that gCDs are discoidal shape. The corresponding high-resolution TEM (HRTEM) image (Fig. 1b) shows the obvious lattices in carbon cores of gCDs, and the distribution of lattice spacing is about 0.21 nm. The lattice spacing value correspond to the (100) inter-planar spacing, demonstrating the almost defect-free graphene crystalline structure [55–57]. Raman spectrum of gCDs (Fig. S2) shows that the intensity ratio (I/D/I) of characteristic D and G bands is about 0.71, and are positioned at 1335 and 1583 cm⁻¹, respectively. The ratio indicates that gCDs are consist of graphene structure (predominantly) and other disorder structure [57,58]. In the 1H NMR spectra of gCDs, the peak at 9.53 ppm in Fig. S3 is the chemical shift of the carboxylic protons [56]. Furthermore, the chemical shift values of aliphatic carbons are present in range from 1 to 5 ppm, which indicated the formation of glycosylated gCDs. As shown in Fig. 1c, it can be seen that the morphology of the prepared gCDs-E is circular or oval nanoparticle with a particles size about 25.5 nm. UV–Vis spectrum of gCDs is shown in Fig. 1d, the two obvious absorption peaks at 216 and 285 nm are attributed to the π→π* transition of C=C–C bond, and the weak absorption band in the range of 300–380 nm belongs to n→π* transition of the carboxylic C=O bond on the surface of gCDs [60,61]. The difference of UV–Vis spectrum for EGCG, gCDs, and gCDs-E at 250–320 nm indicates that EGCG have been successfully anchored on the surface of gCDs. FL excitation and emission spectrum of gCDs (Fig. 1d) exhibits distinct and well-defined peaks at 362 and 445 nm. Fig. 1e and f represent the PL emission of the gCDs and gCDs-E solution under different excitation wavelengths. The gCDs (Fig. 1f) shows two stable emission centers at 445 and 545 nm. However, the as-prepared gCDs-E solutions (Fig. 1f) exhibits distinctive excitation-dependent PL features, which can be attributed to the molecular interaction between EGCG and gCDs, and resulting in red shift of the emission [62]. In addition, after modification with EGCG, the formation of surface emissive traps as well as the varying size distribution of the gCDs caused by EGCG also lead to the wavelength-dependent fluorescence emission property [63,64]. The photoluminescence quantum yield (PLQY) of the gCDs and gCDs-E were calculated to be 12.7% and 9.8%, using the Quantaurus-QY equipment (Fig. S5). The full XPS spectrum presented in Fig. 1g and h shows two peaks at 284.8 and 532.2 eV, suggesting that the gCDs and gCDs-E consist of C and O elements, and the calculated atomic ratios of gCDs and gCDs-E were 57.88%: 42.12% and 44.87%: 55.13%, respectively. In Fig. 1h and k, the high-resolution XPS spectrum of the C 1s band was separated into four peaks at 284.8, 285.8, 286.6, and 288.7 eV, which are assigned to C–C/C=C, C–O, C=O, and COOH, respectively. The O1s band (Fig. 1l) exhibits two peaks at 532.0 and 532.8 eV, respectively, which correspond to C=O and C–O groups. Then, Fourier
transform infrared (FT-IR) was constructed to characterize the functional groups of gCDs and gCDs-E (Fig. S6). In the curve of gCDs (red line) and gCDs-E (purple line), absorption bands at 1642 cm⁻¹ and 1108 cm⁻¹ are corresponding to the stretching vibration of C–O and C–O, respectively. Therefore, hydroxyl and carboxyl are the main functional groups on the surface of gCDs and gCDs-E.

2.2. Inhibition and disaggregation of Aβ by gCDs and gCDs-E

Following, we investigated the potential role of the gCDs and gCDs-E in inhibiting Aβ fibrillation and disaggregating fibrils. TEM results are presented in Fig. 2a and Fig. S7. In the absence of gCDs or gCDs-E, mature Aβ42 and Aβ40 fibrils are obviously observed (Control group, Fig. 2a and Fig. S7a). The same assessments show that the gCDs-E (Fig. 2a and Fig. S7a) can predominantly disaggregate Aβ42 and Aβ40 fibrils into short fragments, with the average length of the fragments shortening from 61 nm to 122 nm after gCDs-E treatment for 24 h, respectively. Corresponding DLS (Fig. S7b and Fig. S8) results also demonstrate the disaggregation ability of gCDs-E. In addition, the fibrillation process of Aβ42 monomers incubated with gCDs or gCDs-E is also effectively suppressed (Fig. 2b), and the average length of the fragments is shortened from 648 nm to 3.6 nm after gCDs-E treatment for 24 h (Fig. 2d). Obviously, more significant disaggregation and inhibition performance of gCDs-E is also exhibited compared with gCDs (Fig. 2c and d). Furthermore, circular dichroism (CD) spectra were used to analyze the change of the secondary structure of Aβ peptides. The non-treated Aβ42 monomers show random structures at 0 h and 30 min (Fig. 2e). However, the typical β-sheet structure of Aβ42 occur from 6 h to 24 h in PBS solution (pH = 7.4), with positive and negative signals at 197 and 218 nm, respectively. Interestingly, the revealed β-sheet structure of Aβ42 treated with the gCDs was significantly inhibited compared with control group (Fig. 2f). Moreover, gCDs-E treated Aβ42 did not show β-sheet structures after 24 h, with only negative signals at 201 nm (Fig. 2f). Corresponding the fractional secondary structures were also analyzed using the algorithm CDNN (Fig. 2g). After treated with gCDs for 24 h, the β-sheet component of Aβ42 decrease from 55.7% to 45.6% and the random coil components increase from 19.3% to 32.3%. The gCDs-E treated Aβ42 shows a drop of β-sheet component from 55.7% to 31.2% and an increase of the random coil components from 19.3% to 35.9%. Furthermore, gCDs and gCDs-E can reverse the secondary structure of Aβ fibrils. As shown

Fig. 1. (a) TEM image and the corresponding size distribution histogram of gCDs. (b) HR-TEM image of gCDs. (c) TEM image and the corresponding size distribution histogram of gCDs-E. (d) UV/Vis absorption spectrum of gCDs in water; the normalized FL emission and excitation spectra of gCDs in water. Fluorescence spectra of (e) gCDs and (f) gCDs-E solution at different excitation wavelengths. (g–i) XPS survey spectrum, high-resolution C 1s, and high-resolution O 1s spectrum of gCDs. (j–l) XPS survey spectrum, high-resolution C 1s, and high-resolution O 1s spectrum of gCDs-E.
in Figs. S9a and b, the most negative peaks of A\(_\beta\) fibrils is typical \(\beta\)-sheet structure at 0 h. After adding gCDs and gCDs-E, the negative peaks of A\(_\beta\) fibrils were significantly reduced and the gCDs-E treated group became more significant than that of gCDs (Fig. S9b). Fig. 2h displays a series of inhibition curves of A\(_\beta\) aggregation in vitro by a thioflavin T (ThT) assay. The fluorescence intensity of non-treated A\(_\beta\) is sharply changed and much strong at 24 h due to the larger amount of A\(_\beta\) fibrillation formation. However, the fluorescence intensity of A\(_\beta\) treated with gCDs significantly decrease and the inhibition efficiency is only 62.97\% (Fig. 2i). gCDs-E treated group shows a weak fluorescence signal, indicating that A\(_\beta\) fibrillation formation is completely suppressed, and the inhibition efficiency of gCDs-E is higher than 90\%. As shown in Fig. 2j, the ThT level of A\(_\beta\) aggregate samples diminished distinctively in the presence of gCDs and gCDs-E during 24 h of incubation, and the disaggregation efficiency of gCDs and gCDs-E were 65\% and 76\%, respectively. We also used AFM to research A\(_\beta\) treated with gCDs and gCDs-E. As shown in Figure 2l, non-treated A\(_\beta\) is mainly long fibrils. A\(_\beta\) treated with gCDs and gCDs-E were unable to form fibrils or other aggregation. In AFM, these A\(_\beta\) fibrils or clusters have average heights of \(~23.7\) nm, compared to heights of \(~3.1\) and \(~1.4\) nm observed for A\(_\beta\) treated with gCDs and gCDs-E (Figure 2m), respectively.

According to the previous reports, hydrophobic and electrostatic
interactions play important roles in the process of interaction between the carbon materials and Aβ peptides [65–68]. Previous study showed that the negative charges of nanomaterials can effectively interact with positively charged His residues of Aβ peptides [65,66]. In this work, gCDs own a similar structure with graphene, and can interact with Aβ peptide by hydrophobic interactions. Zeta potential analysis showed that the surface of gCDs and gCDs-E were both negatively charged (Fig. S10). Therefore, hydrophobic interactions and electrostatic interactions are the two most important factors of inhibiting the Aβ peptide aggregation. More importantly, EGCG can directly bind with unfolded protein and react with free primary amine groups of Aβ peptide, forming a Schiff base, and inducing fibril remodeling [69]. These mechanisms have

![Fig. 3.](image-url) (a) and (b) The growth curves of Candida albicans after adding EGCG or gCDs-E with different concentrations. (c) The corresponding fungi survival rates after 48 h. (d) and (e) Antifungal activities of the EGCG or gCDs-E against Candida albicans evaluated by a standard plate count method.

![Fig. 4.](image-url) (a) The dose dependent cytotoxicity of gCDs and gCDs-E towards neuron cells (SK-N-SH) as determined by CCK-8. (b) Effects of EGCG, gCDs and gCDs-E on cell viability against Aβ-mediated cytotoxicity.
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2.3. Evaluation of gCDs-E for inhibiting Candida albicans

Some research reveals that blood-borne infections with Candida albicans are implicated in diseases as diverse as AD [32]. Here, we verify the inhibition ability of gCDs-E for Candida albicans and further demonstrate a novel strategy of treating AD. Fig. 3a and b shows the growth curves of Candida albicans incubated with EGCG and gCDs-E, respectively. The OD600 values of both EGCG and gCDs-E decreased sharply at 80 μg mL⁻¹ within 24 h. As expected, the antifungal efficiency remarkably increased with the increasing concentration of EGCG or gCDs-E, and the fungi survival rates of Candida albicans treated with EGCG and gCDs-E were only 13.9% and 11.5% at 480 μg mL⁻¹ after 24 h (Fig. 3c), respectively. Then, morphology changes of the Candida albicans were investigated by scanning electron microscopy (SEM). The Candida albicans incubated with gCDs-E shows serious damage in the cell wall and leakage of cellular contents comparing with EGCG treated samples (Fig. S11). However, gCDs have not the antifungal properties based on the growth curves of Candida albicans (Fig. S12). Next, the antifungal activities of EGCG and gCDs-E were evaluated by a standard plate count method using Candida albicans. Remarkably, EGCG and gCDs-E displayed a concentration-dependent antifungal activity against Candida albicans (Fig. 3d and e). Compared with EGCG (suppression effect: 23%), an obvious suppression effect on fungal viability (67.2%) was observed for gCDs-E at a low concentration of 80 μg mL⁻¹. These results indicated that EGCG assembled with gCDs demonstrate effective antifungal functions against Candida albicans.

2.4. Anti-β-secretase toxicity evaluation

In order to evaluate the biological response of the prepared nanomaterials, we first explored its biocompatibility by measuring cytotoxicity in the human neuroblastoma cell line SK-N-SH. SK-N-SH Cells treated with gCDs or gCDs-E for 24 h were assessed by CCK-8 assay for detecting the cell viability [25,70]. Fig. 4a shows the cytotoxicity of various concentrations of the prepared nanomaterials from 1.8 to 160 μg mL⁻¹. Cell viability is observed approximate 85% at a concentration of 160 μg mL⁻¹, which suggests that gCDs-E are almost non-toxic to SK-N-SH cells and can be utilized for further in vitro experiments. To measure the anti-β-secretase toxicity of gCDs-E, gCDs and EGCG, we detected the cell viability of SK-N-SH cells treated with Aβ1-42 in the absence and presence of gCDs-E, gCDs and EGCG. As shown in Fig. 4b, Aβ1-42 alone exhibited obvious toxicity and cell viability was only 62%. However, gCDs-E, gCDs and EGCG were added to suppress the toxicity of Aβ1-42. The gCDs-E treated groups showed remarkably higher cell viabilities than gCDs and EGCG treated groups. This difference in cell viabilities indicated that the combination of EGCG and gCDs resulted in a synergistic anti-β-secretase toxicity effect. In addition, gCDs-E, gCDs and EGCG alone exhibited high cell viability with approximate 100%. gCDs-E showed the highest cell viability (99.2%), close to that of the control group (100%) and was screened as the potential lead drugs for inhibiting Aβ-induced toxicity and treating AD.

2.5. Brain penetration of the gCDs-E in vivo

Blood-brain barrier (BBB), is a widely considered in vivo experiment as a key factor in the treatment of AD. In order to evaluate the ability of gCDs and gCDs-E for overcoming BBB, we intravenously injected a dose of 1 mg mL⁻¹ samples into mice. The mice were sacrificed and the brains were harvested for fluorescence imaging. As shown in Fig. 5a, the higher fluorescence signal in gCDs indicated that this gCDs can reach to the brain compared with PBS treated group. In addition, the fluorescence signal of gCDs-E is also higher than PBS treated group, indicating that gCDs-E also can cross the BBB. The ability of gCDs and gCDs-E for overcoming BBB was further confirmed by immunohistochemical method. As shown in Fig. 5b, the distribution of the gCDs or gCDs-E in the hippocampus was further analyzed. The CLSM images displayed obvious dots of green signals (green fluorescence from gCDs; blue fluorescence from DAPI) in the gCDs and gCDs-E treated group. These results suggested that gCDs and gCDs-E could effectively overcome the BBB in vivo. According to previous report [11,71–73], the main method for nanomedicine to cross the BBB is to modify its surface with glucose. As outstanding candidate ligands for promoting BBB traversal, glucose, the main energy source in the brain, is notable because glucose transporter-1 (GLUT1) is expressed at a remarkably high level compared to many other receptors and transporters in brain capillary endothelial cells [74]. Based on current and previous work [75], the surface of gCDs carbonized by glucose own incompletely reacted glucose structure, which will promote the glucose-functionalized gCDs to cross the BBB through the dependence of glucose transporters.

2.6. Improvement of memory deficits of APP/PS1 mice

As shown in Fig. 6a, the Morris Water Maze test was used to detect whether gCDs or gCDs-E could improve spatial learning ability in APP/PS1 mice. As expected, non-treated APP/PS1 mice showed significant learning deficits. Fig. 6b shows that the learning ability of gCDs-E-treated mice were improved, such as a shorter escape latency after 5 days, longer response time at the target platform position, and a greater possibility of...
reaching the target platform quadrant (Fig. 6b, c and d). More importantly, gCDs-E exhibit significant performance improvement in APP/PS1 mice cognitive ability compared with that of gCDs.

In addition, key factors of AD about Aβ plaques and neuronal loss in the hippocampus were evaluated. Nissl staining analysis (Fig. 7a and c) results reveal that the non-treated and gCDs-treated APP/PS1 mice had few Nissl bodies compared to gCDs-E treated group. In other words, gCDs-E treatment added more neurons with restored integrity, and gCDs treatments is less effective than gCDs-E. An immunohistochemistry analysis was also performed on mouse brains (Fig. 7b and d). The Aβ plaques in the gCDs-E-treated APP/PS1 mice decreased significantly compared with the control and gCDs-treated AD mice, indicating that gCDs-E reduces Aβ plaques. These results indicated that gCDs-E had synergistic therapeutic effects on reducing amyloid plaque and inhibiting neuronal loss in APP/PS1 mice.

2.7. Biocompatibility evaluation of nanomaterials

The cytotoxicity is primary factor for application of nanomaterials in biomedicine. As shown in Fig. S13, the cell viability of the NRK cells remains higher than 90% when the concentration of gCDs and gCDs-E increases from 1.8 to 160 μg mL⁻¹. This result indicates that no significant toxicity was noted in either system at the tested exposure levels. Hemocompatibility is the first-level evaluation before the nanomaterials was administered via tail vein injection [20]. As shown in Fig. S14, hemolysis degree of gCDs and gCDs-E is relatively low and the value of gCDs are 2.459% (80 μg/mL) and 2.76% (160 μg/mL), and the value of gCDs-E are 2.7% (80 μg/mL) and 3.93% (160 μg/mL), respectively. These results indicate that the gCDs and gCDs-E are safe for intravenous administration. The biocompatibility of gCDs and gCDs-E was analyzed in APP/PS1 mice, and the change in body weight after injecting the drug was measured (Fig. 7e). No significant difference in body weight was observed among gCDs or gCDs-E-treated APP/PS1 mice within 17 days. Further, normal mice were treated with different treatments (including PBS, gCDs, and gCDs-E treating), and no abnormal behavior was monitored and the main organs (Heart, Liver, Spleen, Lung, Kidney) of the mice were harvested for histopathological analysis. As shown in Fig. 7f, no obvious pathological abnormalities were detected, which indicated that gCDs and gCDs-E had a favorable biocompatibility, and could be used for further application of AD treatment.

3. Conclusions

In conclusion, we successfully fabricated dual-target nanoassemblies (namely gCDs-E) assembled with EGCG and glycosylated carbon dots, and have proposed an innovative multi-target therapeutic strategy for the treatment of AD. It is demonstrated that gCDs-E can effectively prevent misfolding of Aβ and inhibit its aggregation in vitro, and the inhibition
efficiency is higher than 90%. CCK-8 experiments show that gCDs-E can remarkably reduce Aβ-mediated cytotoxicity. Importantly, gCDs-E also can suppress Candida albicans activity, which could prevent memory loss caused by fungal infection. In vitro and in vivo experiments confirm the gCDs-E's high-biocompatibility and ability of BBB penetration. Furthermore, the gCDs-E can greatly clean Aβ deposition and improve memory impairment in APP/PS1 transgenic AD model mice. Therefore, gCDs-E nanomaterials can serve as a novel nanoplatform, exhibiting great potential therapeutic prospect in the treatment of AD.
Credit author statement

Chaoren Yan and Chaoli Wang: Investigation, Writing-original draft, draft, Writing-review & editing, Visualization, Formal analysis. Yonggang Teng and Xu Shao: Conceptualization, Formal analysis, Investigation, Writing-original draft, Writing-review & editing. Qi Shu: Methodology, Software, Writing-review & editing. Ping Guan: Formal analysis, Writing-original draft. Chaoli Wang: Resources, Software, Formal analysis. Xiaoling Hu, Ping Guan and Yuan Cheng: Supervision, Conceptualization, Resources, Funding acquisition, Project administration. Chaoli Wang and Yuan Cheng: Methodology, Conceptualization, Writing-review & editing, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported financially by the National Natural Science Foundation of China (31771087), Innovation Capability Support Plan of Shaanxi Province (No. 2020TD041), Shaanxi Key Research & Development Program Foundation (2020GY-285). Shaanxi Natural Science Foundation (2021JL-238), Innovation Foundation for Doctor Dissertation of Northwestern Polytechnical University (CXX2021112). We thank the Analytical and Testing Center of Northwestern Polytechnical University for equipment supporting. Thanks to my girlfriend (Ms. Qu) for encouragement.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmbio.2021.100167.

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