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The Development of Clioquinol Labeled-Gold Nanoparticles for the Treatment of Alzheimer's Disease

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Abstract
Clioquinol has emerged as a prominent metal-chelating agent for Alzheimer's Disease. While clioquinol was once a popular antibiotic for skin infections, it has recently been investigated as a potential therapeutic for Alzheimer's Disease. Its metal chelating property can restore metal homeostasis and prevent copper (Cu^{2+}) and zinc (Zn^{2+}) from interacting with amyloid-β (Aβ) peptides. Here, we propose labeling gold nanoparticles with clioquinol as a novel therapeutic approach for Alzheimer's Disease to enable effective delivery of the agent across the blood-brain barrier. Based on previous studies on the individual efficacies of clioquinol and gold nanoparticles, we anticipate that this approach will prevent the formation of Aβ oligomers by disrupting metal-protein interactions. Our proposed clioquinol-labeled gold nanoparticles provide a novel curative approach for Alzheimer's Disease and insights into subsequent therapeutic developments.

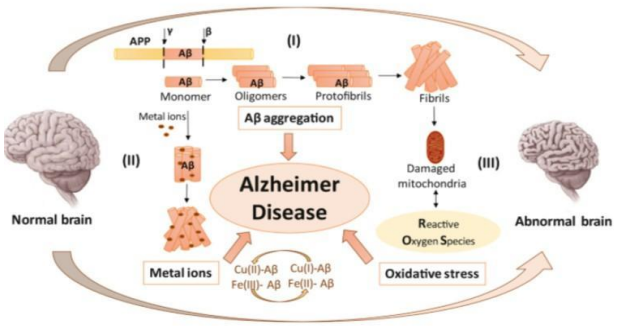
Keywords: Alzheimer's Disease, Amyloid-beta, Clioquinol, Gold Nanoparticles, Metal Chelation, Nanomedicine

1. Introduction

The most common neurodegenerative disease is Alzheimer's Disease (AD), affecting about 6.9 million Americans over the age of 65 and ranking as the seventh leading cause of death in the United States [1]. AD is the most common type of dementia, accounting for approximately 60 to 80 percent of all dementia cases. This disease is primarily characterized by progressive memory loss and cognitive impairment that significantly interfere with daily activities [2]. With age being the largest risk factor for AD, demographic aging imposes a significant risk to the number of people living with AD. Indeed, the number of people with AD is projected to nearly triple by 2060 [3]. Despite the wide prevalence of AD, there is currently no curative therapy due to the complex and elusive nature of the pathophysiology of the disease.

It is crucial to understand key pathophysiological features to develop a curative treatment for AD. The dominating hypothesis related to AD pathophysiology is the "amyloid cascade hypothesis, which posits that the deposition of the amyloid-β (Aβ) peptide in the brain is a central event in [AD] pathology" [4]. Of the multiple pathological mechanisms for AD, it has been observed that there are elevated concentrations of heavy metals such as copper in the brains of AD patients. In AD brains, copper ions (Cu^{2+}) bind to Aβ peptides with high affinity and increase the levels of α-helix and β-sheet structures, thus accelerating the aggregation of Aβ [5]. Furthermore, Cu^{2+} ions enhance fibril formation, and the binding of the copper ions to Aβ increases neurotoxicity. This neurotoxicity is partly attributed to the increased number of reactive oxygen species (ROS), as copper-amyloid complexes produce hydrogen peroxide and lead to the increased production of hydroxyl radicals [6]. Another common heavy metal found in higher levels among AD brains is zinc (Zn^{2+}), which primarily binds to histidine residues at the N-terminus of Aβ, promoting the formation of Aβ oligomers [7]. As copper and zinc are two essential metals that promote the formation of Aβ oligomers that cause neurotoxicity, targeting these metals through metal chelation appears to be a potential therapeutic approach for AD.

Figure 1
Pathophysiology of Alzheimer's Disease



Note. From "Stoichiometry of Heavy Metal Binding to Peptides Involved in Alzheimer's Disease: Mass Spectrometric Evidence," by M. Jureschi, A. V. Lupaescu, L. Ion, B. A. Petre, and G. Drochioiu, 2019, *Advancements of Mass Spectrometry in Biomedical Research*, *1140*, p. 404 (https://doi.org/10.1007/978-3-030-15950-4_23). Copyright 2019 by Springer Nature. [44]

The absence of curative treatment for AD can be pinpointed to the high selectivity of the blood-brain barrier (BBB). To overcome this challenge, we propose conjugating gold nanoparticles (AuNPs) with clioquinol (CQ), a chelator with a high affinity for copper and zinc ions. Gold nanoparticles have anti-inflammatory and antioxidant properties, modulating oxidative stress and detecting ROS [8]. CQ is commonly used as a topical antiseptic for skin infections, but its ability to chelate copper and zinc renders it a potential treatment for AD. While CQ has high liposolubility and can cross the BBB, only a small portion of it delivered reaches the brain, as indicated by how only 7% of CQ was found in the cerebrospinal fluid (CSF) after intraperitoneal injection in golden hamsters [9]. To address this limitation, we suggest the conjugation of AuNPs that can easily cross the BBB with CQ to chelate copper and zinc and act as a therapeutic agent.

Moreover, we plan to integrate fluorochromes with gold nanoparticles to ensure that clioquinol-labeled gold nanoparticles cross the BBB and reach the metal binding sites on Aβ peptides incorporated. Consequently, we ultimately propose the development of clioquinol-labeled gold nanoparticles, along with fluorochromes, to both detect AD biomarkers and treat AD.

2. Background

Despite the numerous hypotheses that aim to explain the etiology of AD, there is still no cure for this multifactorial disease. However, some drugs help alleviate AD symptoms by inhibiting cholinesterase to prevent the breakdown of acetylcholine, as the AD brain produces less acetylcholine [10]. Another common medication is memantine, an N-methyl-D-aspartate (NMDA) antagonist. Memantine only decreases AD symptoms by regulating glutamate, which typically leads to nerve cell death when present in excessive amounts [10]. Regarding treatment, the United States Food and Drug Administration (FDA) recently approved lecanemab and donanemab to target Aβ fibrils and plaques. The effects of these drugs, however, have not been observed for prolonged periods and are only designed to slow down the progression of AD rather than cure it.

Due to the absence of curative treatment, new treatment modalities are currently being explored for AD. The latest treatment strategies include gene therapy, immunotherapy, peptidomimetics, and metal chelation [11]. Metal chelation is particularly interesting, for metal ions such as Cu^{2+} and Zn^{2+} are critical for the pathogenesis of AD. Aβ peptides can bind Cu^{2+} with high affinity and become an Aβ radical that can oxidize lipids and proteins, generating Cu^{+} and superoxide, which can immediately produce hydrogen peroxide [12]. When Aβ binds to Zn^{2+}, while the formation of oligomers is accelerated, it does not cause oxidative damage. Nevertheless, when the two transition metals interact with Aβ peptides, the formation of oligomers is precipitated.

Metal chelation can disrupt such metal-protein interactions and inhibit the formation of Aβ oligomers and the aggregation of Aβ fibrils. In concordance with the amyloid cascade hypothesis, targeting the formation of Aβ oligomers through metal chelation can be a therapeutic approach for AD. To do so, CQ is to be used, for it can act as a copper and zinc chelator [13]. The efficacy of clioquinol as a therapeutic agent for AD has been explored; indeed, Ritchie et al. found that the clioquinol-treated group had significantly decreased plasma Aβ42 levels while the placebo group had increased plasma Aβ42 levels 20 weeks after administration in a pilot phase

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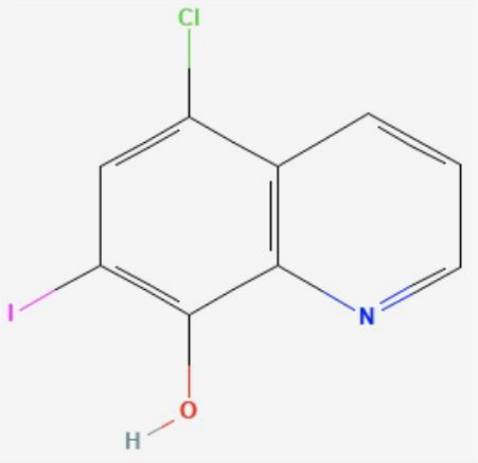
2 clinical trial [14].

Even though CQ is chemically known as a metal chelator, counterintuitively, when CQ was administered to Tg2576 transgenic mice modeling AD, copper levels in the brain increased by 19% and zinc by 13% while Aβ deposition was inhibited [15]. To explain this finding, Treiber et al. hypothesized that CQ may redistribute copper from Aβ to other neurons or facilitate "the uptake of CQ-copper complexes in the brain" [15]. Such explanations are feasible since CQ is lipophilic and can cross the BBB.

Yet, a significant drawback of CQ is neurotoxicity and its association with subacute myelo-optic neuropathy (SMON), a syndrome characterized by hemorrhagic diarrhea and paralysis of the lower limbs [16]. Fortunately, toxicity studies revealed that only high doses of CQ result in neurotoxicity; in humans, the typical dose is "1.5–2 g/day (~25–30 mg/(kg day))," and the maximum tolerated dose is "3.5 g/day (~50 mg/(kg day))" [17]. Furthermore, since symptoms of SMON syndrome are associated with vitamin B12 deficiency, it is advised that patients receiving chronic doses be given vitamin B12 supplements [13].

Figure 2
Chemical Structure of Clioquinol



Note. From "PubChem Compound Summary for CID 2788, Clioquinol," by the National Center for Biotechnology Information, 2024 (https://pubchem.ncbi.nlm.nih.gov/compound/2788#section=2D-Structure). Courtesy of the National Library of Medicine. [45]

The high lipophilicity of CQ enables it to cross the BBB, but only a small portion relative to its lipophilicity reaches the brain. For instance, the brain-plasma ratio of CQ was about 20% after CQ administration in golden hamsters, and only 7% was found in the ventricular CSF an hour after intraperitoneal dosing [9].

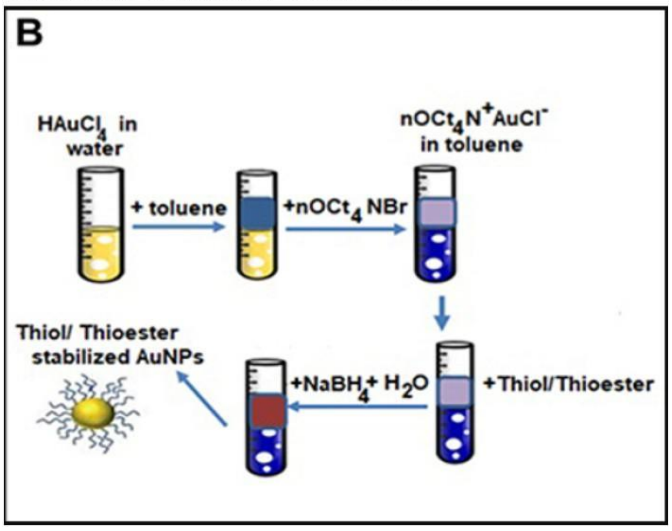
To improve the delivery of CQ across the BBB, AuNPs are to be labeled with CQ, as they have high versatility and biocompatibility. As size is a crucial parameter for effective delivery, AuNPs are potential therapeutics due to the ease of surface modification to cross the BBB [18]. In particular, 2 nm AuNPs can not only cross the BBB but are also readily taken up by cells and even the nucleus [19]. Further, AuNPs can increase the bioavailability of CQ by enhancing aqueous solubility and increasing half-life to ensure that CQ is delivered to its targeted site of action [20]. Such can be achieved due to the high surface functionality of AuNPs, which means that they have a large surface area, enabling numerous molecules to attach to the surface. In other words, AuNPs can be tuned for various purposes by the attachment of specific molecules. Hence, employing the versatility of AuNPs, we propose labeling AuNPs with CQ to facilitate the delivery of CQ across the BBB and ensure precise targeting

3. Approach

3.1 Synthesizing Gold Nanoparticles

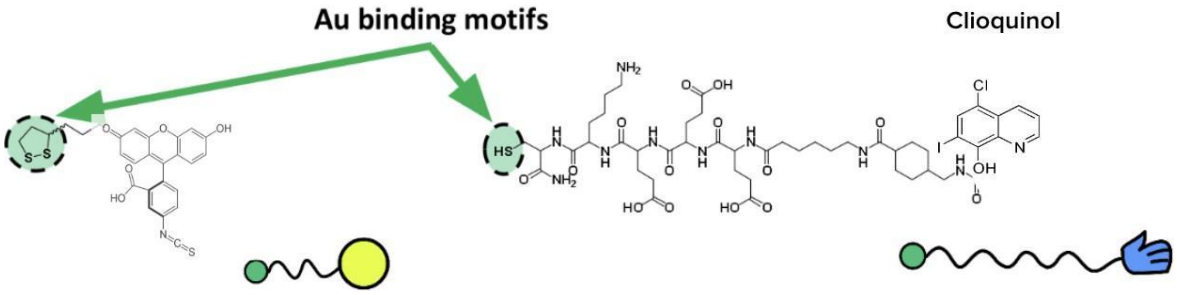
To produce AuNPs of 2 nm, the Brust-Schiffrin method will be applied to create alkanethiol-stabilized AuNPs. This method typically involves two processes for the reduction of chloroauric acid ($HAuCl_4$), utilizing tetrabutylammonium bromide (TOAB) as a phase transfer catalyst and sodium borohydride ($NaBH_4$) as the reducing agent, along with an alkanethiol [21]. Chloroauric acid reduction increases the stability of AuNPs due to the effect of strong thiol-gold interactions, allowing the ligand and fluorochrome complex to attach [22]. The protein targeting group will be composed of sulfur molecules, including disulfide bonds with CQ ligands at the periphery. The signaling group will be composed of bisulfide (HS^-) and fluorochrome. The attachment of the protein components to the synthetic gold particle will be characterized by self-assembled monolayer (SAM) absorption. SAM absorption is typically composed of nanoparticles that have a strong affinity to the mediated solution. We can use the gold-sulfur bond to immobilize the protein particles containing CQ and fluorochrome, anchoring them to the synthetic gold particle and preventing AuNPs from aggregating [23].

Figure 3
Brust Method for the Synthesis of Gold Nanoparticles



Note. From "A Review on the Synthesis and Functionalization of Gold Nanoparticles as a Drug Delivery Vehicle," by S. J. Amina and B. Guo, 2020, *International Journal of Nanomedicine*, *15*, p. 9825 (https://doi.org/10.2147/ijn.s279094). CC BY-NC. [21]

Figure 4
Components of Clioquinol-Labeled Gold Nanoparticles



3.2 Quantification of the Efficacy of CQ-Labeled AuNPs

We plan to utilize in vivo mouse models to quantify the drug efficacy. Particularly, Tg2576 mice are to be used, as they are genetically modified to overexpress the human beta-amyloid precursor protein 695 (beta APP695). These mice models show features of AD such as Aβ plaques, vascular amyloid, and loss of dendritic spines only at six months [24].

First, Tg2576 mice will be obtained from Taconic Biosciences. Then, we will deliver clioquinol-labeled gold nanoparticles either through oral ingestion or intraperitoneal injection. The levels of Cu^{2+} and Zn^{2+} will be observed on days 1, 5, and 10 following the administration of CQ-labeled AuNPs. Subsequently, the brains of the mice will be excised and dissolved in aqua regia. The dissolved solution will then be diluted with basic diluents with a dilution factor between 10 and 50. This diluted sample is to be analyzed through inductively coupled plasma mass spectrometry (ICP-MS), a technology that can simultaneously measure multiple elements [25]. After the sample is introduced into the ICP-MS system, the nebulizer will convert it into a fine aerosol, which will be transported into the plasma torch, where the sample will be converted into an ionizable form. In the plasma torch, argon gas (Ar) will be ionized at temperatures as high as 10,000 K [25]. At such high temperatures, the sample will break down into its constituent atoms and be further ionized to form ions. These ions will then be analyzed through a mass spectrometer, which will separate ions based on their mass-to-charge ratio [25]. In particular, we will quantify the levels of copper and zinc and compare them to those in wild-type mice.

3.3 Plan B: Cobalt(III) Schiff Base Complexes in Microbubbles

3.3.1 Modification of Microbubbles with Cobalt(III) Schiff Base (Co(III)-sb) Complexes

Although producing CQ-labeled AuNPs has a high potential to be successful, we may encounter unexpected outcomes. Therefore, an alternative method to exploit these complexes is described. Co(III)-sb

complexes have been shown to irreversibly inhibit Aβ peptide aggregation by binding to the terminal histidine residues on the Aβ peptide. This simultaneously displaces Cu^{2+} and Zn^{2+} binding to the peptide [26]. To overcome transport limitations regarding the BBB, we will use microbubbles as vehicles to enter the brain. Using focused ultrasound, mechanical stress will be applied to release the Co(III)-sb agents [27].

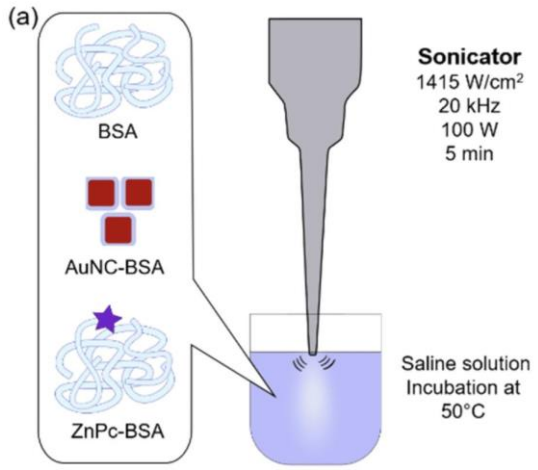
3.3.2 Components of Microbubbles

Albumin microbubbles (MBs) filled with perfluorocarbon will bind to Co(III)-sb complexes, transferring them across the BBB. Fluorocarbon will reduce osmotic pressure in MBs, thus providing long-term stability [28]. To minimize immune responses, the microbubble shell will be composed of bovine serum albumin (BSA), as BSA and human serum albumin inside the blood plasma have high structural similarity [29].

3.3.3 Fabrication of Microbubbles

The sonication method typically produces MBs with suitable coatings, enclosing the materials inside the bubble with an ultrasound probe [28]. A salt-contained solution will be mixed with 150 mg of BSA to prepare MBs with BSA shells. The atmosphere above the solution will be filled with perfluorocarbon. The solution with BSA will be heated at about 50°C to lower the surface tension. Then, the solution will be sonicated by 100W for 5 minutes by the sonicator, producing MBs containing perfluorocarbon.

Figure 5
Sonication Method of Microbubbles Preparation



Note. From "Air-Filled Microbubbles Based on Albumin Functionalized with Gold Nanocages and Zinc Phthalocyanine for Multimodal Imaging," by E. A. Maksimova, R. A. Barmin, P. G. Rudakovskaya, O. A. Sindeeva, E. S. Prikhozhdenko, A. M. Yashchenok, B. N. Khlebtsov, A. A. Solovev, G. Huang, Y. Mei, K. K. Dey, D. A. Gorin, 2021, *Micromachines*, *12*(10), p. 1161 (https://doi.org/10.3390%2Fmi12101161). CC BY 4.0. [29]

3.3.4 Microbubble Separation to Collect 1 μm Diameter Microbubbles

The removal of larger air foam or bubbles is essential to collect MBs of 1 μm inside the solution. Borrelli et al. introduced a method using a "Luer-lock syringe fitted with a blunted 1-1/2 inch long 18 g needle" that collects the MB-contained solution [30]. This method removes larger foams and bubbles by tapping the syringe against a solid surface and using an aspirator. The capped syringes with 1 μm and other sized MBs will be stored plunger-up in racks. Then, a low milky fraction containing the 1 μm MBs will be formed after one to six hours. If approximately 80 percent of the collected solution contains 1 μm MBs, it will indicate a successful MB separation.

3.3.5 Peptide Coupling

We will use a protein coupling reagent to produce a peptide bond between Co(III)-sb complexes and BSA, converting the carboxyl group (-OH) into a leaving group. Co(III)-sb complexes will react with the protein coupling reagent, dicyclohexylcarbodiimide (DCC); this will deprotonate Co(III)-sb and enable it to attach to DCC [31]. Then, BSA will be attached to the combined molecule, creating a leaving group with DCC by the transfer of electrons. Eventually, DCC with supplied electrons will detach due to the charges, thereby creating a peptide bond between the Co(III)-sb complex and BSA.

3.4 Blood-Brain Barrier (BBB) Assay

To overcome the transport limitation of current AD treatments across the BBB, we will test the permeability of our proposed approach using an in vitro BBB assay. This assay involves a triculture model composed of induced pluripotent stem cell (iPSC)-derived human brain epithelial cells, astrocytes, and pericytes [32]. The BBB assay kit (RBT-24H, BBB Kit™) is to be purchased from PharmaCo-Cell Company Ltd [33]. With the assay kit, we will test the permeability of CQ-labeled AuNPs and observe if any leaches through. Then, through mass spectrometry, we will detect and quantify the amounts of Cu^{2+} and Zn^{2+}.

The BBB assay includes cultured rat brain microvascular endothelial cells and rat brain pericytes separated by a macroporous Millicell® membrane, which are precultured with astrocytes maintaining tight junctions [33]. The BBB model will be incubated at 37°C and 5% CO_2 environment for 4-5 days to regenerate tight junctions. After rinsing the BBB cell layers with the assay medium, AuNPs will be injected into the apical side of the BBB layers. The cells will be cultured for a few hours and examined at 30-minute intervals. To verify the permeability, we will observe the transportation of AuNPs to the basolateral side of the cell layers by a fluorescence detector. Using the permeability coefficient (P_{app}), we will quantify the permeability of AuNPs across the BBB.

$$P_{app} = \frac{V}{A \times [C]_{apical}} \times \frac{\Delta[C]_{basolateral}}{\Delta t} \quad (1)$$

($[C]_{apical}$: initial concentration of fluorescent nanoparticles in apical side; $\Delta[C]_{basolateral}$: differential concentration of fluorescent nanoparticles in basolateral side; A: surface area of membrane; V: medium volume in basolateral side)

4. Expected Results

4.1 BBB Permeability

Based on previous studies that have shown the ability of AuNPs and CQ to cross the BBB, it is anticipated that CQ-labeled AuNPs will also be able to do so. Using the BBB permeability assay, we expect the majority of the CQ to pass the barrier and reach Aβ peptides. While not all of the CQ delivered may reach the target, with fluorochromes, we expect that precise detection of the target can be made, enabling the majority of the CQ to reach its targeted site of action.

4.2 Concentrations of Cu^{2+} and Zn^{2+} (μg metal per g^{-1} lyophilized tissue weight)

After accurate detection, we expect that the administration of CQ will produce a statistically significant reduction in the levels of Cu^{2+} and Zn^{2+} after ICP-MS analysis. Moreover, we anticipate post-mortem examinations of Tg2576 mice brains to reveal a significant reduction in Aβ oligomers and plaque formation.

Before treatment, we predict that the Tg2576 mice will have a Cu^{2+} concentration of around 16 μg g^{-1} in the cortex and 20 μg g^{-1} in the hippocampus, and the wild-type mice will have around 11 μg g^{-1} in the cortex and 14 μg g^{-1} in the hippocampus. Post-treatment with CQ-labeled AuNPs, we expect the copper concentration of the Tg2576 mice to decrease to the same levels as the wild-type mice. Alternatively, while the Cu^{2+} concentration may not decrease to baseline levels, we expect that it will still have a statistically significant decrease.

The initial Zn^{2+} concentration we anticipate for the Tg2576 mice will be approximately 75 μg g^{-1} in the cortex and 84 μg g^{-1} in the hippocampus, and that of the wild-type mice will be approximately 52 μg g^{-1} in the cortex and 58 μg g^{-1} in the hippocampus. After treatment with CQ-labeled AuNPs, we expect the Zn^{2+} concentration to drop to equivalent levels with the wild-type concentration or have a statistically significant decrease.

4.3 Toxicity

In terms of toxicity, we expect that the administration of low doses of CQ will not impose neurotoxic effects, especially when coupled with vitamin B12 supplements. Given that the dose of CQ does not exceed 3.5 g/day, it is assumed that no significant neurotoxic effects will be present for those weighing around 60 to 70 kilograms (132 to 154 pounds). Even though there may be side effects, including nausea, mild diarrhea, and dizziness, with proper doses, we expect that there will not be significant neurotoxic effects such as SMON syndrome.

4.4 Longitudinal Results

From a longitudinal perspective, it is anticipated that fewer Aβ peptides will form into oligomers, and the generation of reactive oxygen species will be reduced. With controlled administration of clioquinol, we expect that subjects will perform better on cognitive tests such as the Montreal Cognitive Assessment (MoCA) for humans and the Morris water maze for mice.

5. Discussion

5.1 Permeability Assay

Based on the chemical properties of CQ and the size of AuNPs, small concentrations of CQ and AuNPs can cross the BBB through passive diffusion. CQ is a lipophilic molecule with a molecular weight of 305.5 g/mol, making it a small molecule that can easily cross the BBB. Moreover, our proposed AuNPs have a size of 2 nm, enabling them to readily diffuse through the BBB. Indeed, Sela et al. have demonstrated that 2.5 nm AuNPs can spontaneously cross the BBB [34]. By labeling AuNPs with CQ, CQ can easily cross the BBB, bind to Cu^{2+} and Zn^{2+}, and chelate them.

5.2 Metal Concentrations

On AuNPs, CQ in the targeting group will act as a ligand, binding to Cu^{2+} and Zn^{2+} and chelating them. CQ increases endocytosis, inhibiting the formation of copper-dependent oligomers [35]. For instance, microarray results indicated that CQ can sequester Cu^{2+} at the cellular membrane and decrease the level of metals in the cytoplasm [36]. The metal chelating property of CQ will reduce the concentrations of Cu^{2+} and Zn^{2+} and prevent them from binding to Aβ peptides. As such, metal homeostasis can inhibit the formation of Aβ oligomers.

5.3 Toxicity

When CQ is administered at high doses, it has a pro-oxidant effect that increases malondialdehyde and damages neurons [37]. Malondialdehyde is a product of lipid peroxidation that reacts with deoxyribonucleic acid (DNA), forming exocyclic adducts that have mutagenic properties [38]. Nevertheless, CQ concentrations up to 10 μM do not impact cell viability [39]. Therefore, with proper doses, CQ would not cause neurotoxicity and effectively prevent Aβ oligomer formation.

5.4 Efficacy

The inhibition of Aβ oligomer formation through metal chelation would reduce neuronal damage and death, thereby maintaining cognitive functions. Our proposed approach is expected to inhibit AD from progressing and potentially cure AD by targeting the underlying pathology.

Indeed, after five weeks of CQ treatment in Tg mice, Analysis of Variance (ANOVA) tests revealed that there was a significant reduction in the escape latency in the Morris water maze task ($P < 0.0001$) [40]. They demonstrated how CQ treatment significantly improved cognitive and memory functions in mice, illustrating the efficacy of CQ in enhancing cognitive abilities within a relatively short period. As such, based on previous studies on the efficacy of CQ, we anticipate that CQ-labeled AuNPs can significantly improve cognitive function among AD patients.

6. Conclusion and Future Directions

Here, we have proposed labeling AuNPs with CQ as a novel therapeutic approach for AD. Despite the enactment of the National Alzheimer's Project Act (NAPA) in 2011 and annual investments of more than $3.8 billion, there is still an absence of curative treatment for AD [41]. Not only is this due to the sporadic and multifactorial nature of AD, but it is also due to the high selectivity of the BBB. As such, we proposed CQ-labeled AuNPs as a potential therapeutic for AD. Leveraging the metal-chelating properties of CQ and the biocompatibility of AuNPs, we target the restoration of metal homeostasis to inhibit the formation of Aβ oligomers. In contrast to traditional drugs for AD, CQ-labeled AuNPs can cross the BBB and have relatively low toxicity concerns when given proper doses. To explore the efficacy of CQ-labeled AuNPs, we suggest in vitro BBB permeability assays and in vivo mice models.

Future studies should focus on longitudinal studies to observe the long-term effects of CQ and AuNPs. In particular, we suggest that future studies investigate toxicity and efficacy and utilize cognitive tests. Furthermore, future studies can investigate the potential of gene therapy for AD. Specifically, they can focus on the possibility of clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated (Cas) 9 to edit the apolipoprotein E (APOE) gene. While most people carry two APOE ε3 alleles, about 15 to 25 percent carry one APOE ε4 allele, and 2 to 5 percent carry two copies [42]. APOE ε3 has a neutral risk for AD, but having one copy of the APOE ε4 triples the risk for AD, and having two copies nearly increases the risk by twelvefold [43]. Intriguingly, the two differ by a single amino acid at position 112, making CRISPR-Cas9 a promising technology to aid in the precise editing of the APOE gene. Additionally, future studies can utilize CRISPR-Cas9 to edit the APOE ε4 gene to APOE ε2, which has a protective effect on AD. Such research could contribute to developing optimal preventative and therapeutic strategies for AD.

Even though substantial progress is being made to slow down the progression of AD, the absence of curative treatment necessitates further research into new therapeutic approaches. By labeling gold nanoparticles with clioquinol, we have developed a promising approach to cure AD by providing insights into the role of metal dyshomeostasis in AD pathology and targeting Aβ peptides.

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