

Review Article

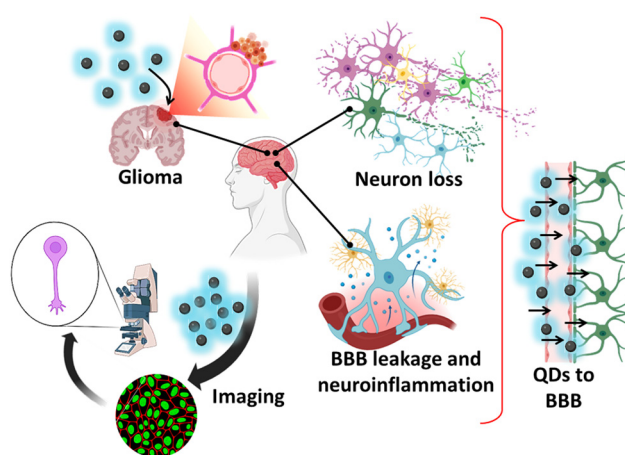
Muhanna K. A. Al-Muhanna*, Amani Ahmed Alghamdi, Bahauddeen Alrfaei, Mohammad Afzal, Reema Al-Subaiee, and Rania Haddadi

Surface-engineered quantum dot nanocomposites for neurodegenerative disorder remediation and avenue for neuroimaging

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Abstract: This review investigates the potential of surface-engineered quantum dot (QD) nanocomposites in the treatment of neurodegenerative disorders and their use in neuroimaging. QDs possess distinctive properties such as adjustable fluorescence and adaptable surface modification, making them useful for both targeted drug administration and precise imaging in the complex nervous system. The report provides a concise overview of progress and obstacles, with a particular focus on concerns regarding biocompatibility, potential toxicity, and the ability to cross the blood–brain barrier. The importance of continuous research in surface engineering, biocompatibility investigations, and standardization of synthesis procedures is emphasized as essential measures to overcome these obstacles. Although there are challenges, the review highlights the significant potential of surface-engineered QD nanocomposites to transform our understanding of neurodegenerative disorders and improve neuroimaging techniques. This could lead to better diagnostic and therapeutic approaches for neurological health in the future.



Graphical abstract

Keywords: surface engineered, quantum nanostructures, nanocomposite, biocompatibility, neuroimaging, healthcare

1 Introduction

Neurodegenerative disorders encompass a wide range of debilitating conditions characterized by a progressive loss of the nervous system, namely the neurons in the brain. Disorders including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease are characterized by a variety of symptoms, including cognitive decline, motor dysfunction, and, occasionally, psychological abnormalities [1–3]. The fundamental cause of the condition frequently entails the buildup of abnormal proteins or the deterioration of particular groups of nerve cells. Although age is a notable risk factor, many neurodegenerative illnesses can affect individuals at a younger age as a result of genetic factors. At present, there are no conclusive therapies for these conditions. Thus, it is crucial to recognize and manage them early. Current research endeavours aim to elucidate the complex mechanisms behind neurodegeneration, providing optimism for advancements in treatment and

* **Corresponding author: Muhanna K. A. Al-Muhanna**, Materials Science Research Institute, King Abdulaziz City for Science and Technology (KACST), Riyadh, 11442, Saudi Arabia, e-mail: mmuhanna@kacst.gov.sa

Amani Ahmed Alghamdi: Department of Biochemistry, College of Science, King Saud University, Riyadh, 11451, Saudi Arabia

Bahauddeen Alrfaei, Reema Al-Subaiee: Stem Cells and Regenerative Medicine Unit, Blood and Cancer Research Department, King Abdullah International Medical Research Center (KAIMRC), Riyadh, 11481, Saudi Arabia; College of Medicine, King Saud Bin Abdulaziz University for Health Sciences (KSABU-HS), Ministry of National Guard-Health Affairs (MNGHA), Riyadh, 11481, Saudi Arabia

Mohammad Afzal: Department of Chemistry, College of Science, King Saud University, Riyadh, 11451, Saudi Arabia

Rania Haddadi: Department of Zoology, College of Science, King Saud University, P.O. Box 2455, Riyadh, 11451, Saudi Arabia

preventative approaches [4,5]. Technological advancements, such as brain imaging and biomarker identification, play a role in the early detection and monitoring of disease progression. Furthermore, promising improvements in the field of therapy, such as targeted pharmaceuticals and gene-based treatments, offer the potential to alter the progression of many conditions. The significance of promptly identifying and addressing neurodegenerative diseases cannot be exaggerated, as these disorders typically progress gradually and covertly. Timely diagnosis enables prompt intervention and the adoption of techniques to effectively manage symptoms, thereby enhancing the quality of life for affected persons [6–8]. Early identification is crucial for protecting cognitive function and motor ability in numerous neurodegenerative illnesses, as irreparable damage gradually develops over time [6]. Furthermore, the prompt recognition enables the timely implementation of suitable medical, psychological, and supportive measures, empowering patients and their families to strategize for the future. Moreover, timely identification plays a crucial role in promoting progress in scientific investigations by offering a chance to investigate potential treatment interventions and strategies that can influence the course of the disease [9]. As the quest for targeted medicines and personalized medicine persists, early detection remains a fundamental aspect of the overall strategy to tackle the difficulties presented by neurodegenerative diseases.

Nanomaterials have demonstrated great potential in the field of treating neurodegenerative disorders [10]. Nanostructure materials such as nanotubes, nanowires (1D), and graphene, as well as transition metal dichalcogenides (2D), contain distinct characteristics that make them appealing for therapeutic applications [11–15]. Their extensive surface area, tuneable characteristics, and capacity to engage with biological systems on a nanoscale level present promising prospects for medication administration, imaging, *etc.* [16–18]. Nevertheless, these nanomaterials possess certain limitations that require meticulous consideration for their effective implementation in the treatment of neurodegenerative disorders. One significant issue is the potential toxicity of these nanomaterials. Furthermore, biodistribution and clearance concerns impede their successful usage, as ensuring that nanomaterials reach specific areas in the brain while avoiding accumulating in key organs is difficult. Nanomaterials face a significant challenge in efficiently crossing the blood–brain barrier (BBB) to access neural tissue [19]. Ensuring long-term stability is a significant challenge, as nanomaterials have the potential to aggregate or degrade over time, which can compromise their effectiveness in therapy. To fully exploit the potential of different nanomaterials in developing safe and effective therapeutics for neurodegenerative illnesses, it is essential to address these constraints as research advances.

Quantum dots (QDs) constitute a cutting-edge technology with great potential for applications in diverse sectors, such as medicine and neuroscience [20–24]. The tiny semiconductor particles often made of cadmium selenide or indium phosphide display distinctive optical and electrical characteristics due to quantum confinement effects. QDs in the field of neuroimaging have attracted significant interest due to their capacity to potentially transform the visualization and monitoring of brain structures [25,26]. Due to their small dimensions and tuneable optical characteristics, they are highly suitable for marking and visualizing specific cells or structures within the intricate neural network [27,28]. The functionalization of QDs to target particular biomolecules permits the labelling of neurons and other relevant components with extreme precision and selectivity. This capacity has tremendous potential for enhancing our comprehension of brain anatomy and operation. Moreover, the durability and luminescence of QDs render them highly valuable tools for conducting extended imaging investigations, providing a vital understanding of the ever-changing processes occurring within the brain. As research advances in this area, QDs could become essential instruments for high-resolution and real-time neuroimaging, providing new opportunities to investigate brain disorders and aiding the creation of precise therapeutic approaches [21,29]. Neuroimaging techniques and the study of neurodegenerative diseases stand to benefit greatly from surface-engineered QD nanocomposites, which are highlighted in the review as having enormous promise. This review focuses on the innovative use of surface-engineered QDs for both repair and imaging in neurodegenerative illnesses. The uniqueness of this strategy is found in the versatile abilities of QDs, which provide exceptional optical characteristics, allowing for enhanced imaging precision and accuracy in identifying initial pathogenic alterations in neural tissues. QDs, unlike conventional imaging methods, can be customized with precise surface alterations that improve their compatibility with living organisms and allow them to be delivered specifically to damaged areas of the brain. This enables both diagnostic and therapeutic interventions. Incorporating QDs into therapeutic frameworks offers a revolutionary approach to both monitoring and reducing the progression of diseases, particularly neurodegenerative diseases. This has the potential to significantly change how we treat these types of diseases. This study highlights the notable progress and potential of QDs in addressing current constraints in neuroimaging and treatment. It positions QDs as an innovative and adaptable tool in combating debilitating neurological illnesses.

2 Surface engineering of QDs

Surface engineering of QDs plays an essential role in tailoring their characteristics for specific applications in

optoelectronics, bioimaging, and theranostics [30–34]. It is widely acknowledged that surface passivation with functional groups not only creates surface defects that give rise to fluorescence but also offers reactive sites for targeted functional modifications. Utilizing these reactive groups, a wide range of materials, including organic, polymeric, inorganic, and biological substances, can be attached to QD surfaces [35–37]. This is achieved through covalent bonds, hydrogen bonds, and electrostatic interactions [38,39]. These

attachments serve as a foundation for targeted sensing, drug delivery, and other specialized functions [40]. Experimental evidence indicates that colloidal QDs comprise an inorganic core (that includes inner atoms) that retains the bulk crystal lattice's geometry, an outer inorganic atom surface (which includes outer atoms) that has a distinct morphology from the inner core, and a layer of ligands bonded to the outer surface [41]. The QD's photophysical properties are determined by its core, which is influenced by factors such as

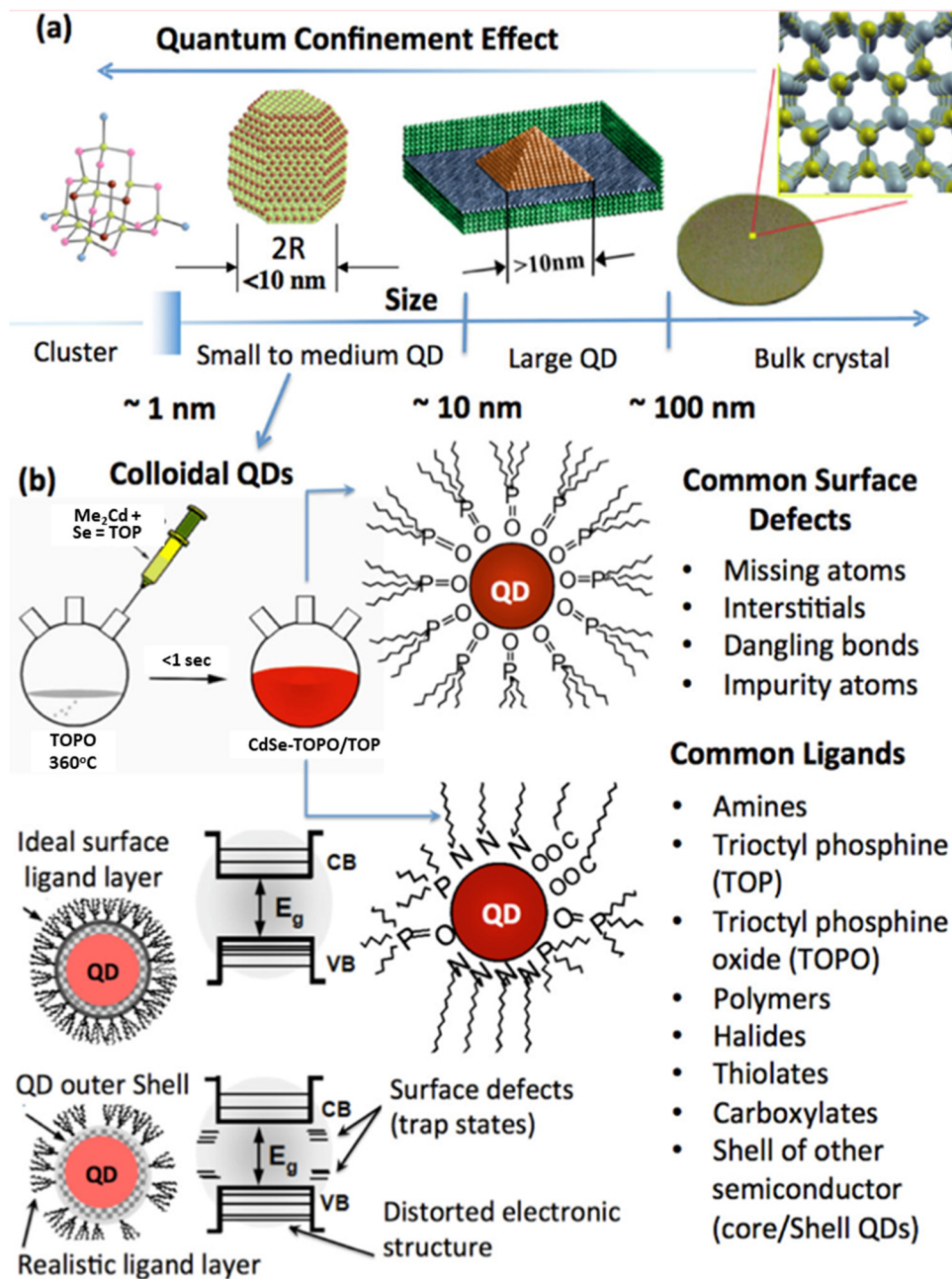


Figure 1: (a) Graphical representation for classification of clusters, QDs, and bulk and (b) the effect of ligand passivation on QD band gap. Reproduced with permission from Kilina *et al.* [42], © 2015 American Chemical Society.

bulk materials, shape, and confinement effects. On the other hand, the surface of the QDs can also have an impact on these properties. Figure 1 depicts the classification of nanostructures into two limiting cases: clusters and bulk crystals, as well as the potential effects of surface and ligand layers on their electronic structure.

There is a distinct difference between bulk materials and QDs. QDs are nanostructures that fall within the range where quantum confinement effects come into play. In other words, the size of the QD is such that the exciton Bohr radius is either equal to or greater than the QD radius. The nanosystem's electronic structure is determined by its geometry. This includes factors such as the size of the system, which can have confinement effects, as well as the stoichiometry and the interface between passivating ligands and the QD surface, which can have surface effects.

Cho *et al.* successfully devised a simple and efficient technique for controlling precisely the surface characteristics of luminescent graphene quantum dots (GQDs) [43]. The surfaces of the hydrophilic GQDs were modified based on the number of grafted hydrophobic hexylamine during the synthesis process. Unlike the pure GQDs, the modified GQDs can stabilize oil-in-water Pickering emulsions and submicron-sized colloidal particles in mini-emulsion polymerization. The authors demonstrated (Figure 2) full-range control of the surface properties of the GQDs, ranging from very hydrophilic to completely hydrophobic, using a series of four modified GQDs with gradually increasing levels of grafted hexylamine. The efficiency of modified GQDs as particle surfactants in various immiscible blends was investigated using a controlled hydrophilic/hydrophobic

balance. Furthermore, all emulsions and particles stabilized by GQD surfactants were highly stable and fluorescent, providing a successful example of synergistic inclusion of the unique GQD characteristics into composites. The synthesis of QDs-antibody bioconjugates (QDs-mAb) involved the incorporation of polyethylene glycol (PEG) cross-linkers and Fc-shielding mAb fragments [44]. This was done to enhance the circulation times and targeting efficiency of the bioconjugates *in vivo*. When the QDs-mAb directed against cell adhesion molecules was used to incubate endothelial cell cultures and Fc-mediated interaction was reduced, the microscopy results showed increased specificity for the molecular targets.

There are different surface engineering procedures that are utilized to improve stability, biocompatibility, and usage [44]. QD surfaces can be tailored through ligand exchange, encapsulation with polymers, and inorganic shell growth processes. These methods enhance the QD's ability to dissolve in various solvents and offer chances for interaction with biomolecules or other functional groups, allowing precise manipulation of their interactions with biological systems or other materials [43]. Furthermore, surface engineering can efficiently tackle issues such as photobleaching and toxicity, hence improving the use of QDs in various future technologies.

The incorporation of green biomaterial concepts in the production of QDs signifies a notable progress in terms of environmental sustainability and biomedical safety [45]. Conventional QD synthesis processes commonly employ heavy metals and toxic solvents, resulting in the production of dangerous waste and posing possible health hazards. The

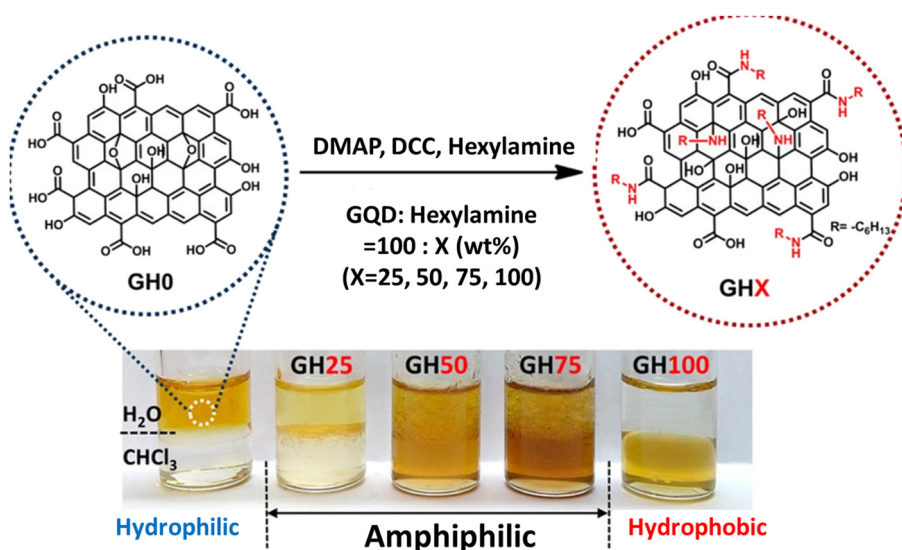


Figure 2: Method of preparing surface-engineered GQDs using hexylamines. Reproduced with the permission from Cho *et al.* [43], © 2015 American Chemical Society.

principles of green biomaterials promote the utilization of renewable, non-toxic resources and ecologically friendly procedures. This move not only decreases the environmental impact of QD manufacture but also improves their ability to interact with living organisms, making them more secure for use in medical applications, such as seeing biological structures and administering medication [31,35,46]. Green QDs are specifically engineered to retain the desirable traits of traditional QDs, such as strong luminescence and adjustable electrical properties, while mitigating the potential risks to the environment and human health [47]. Green QD production utilizes natural precursors and aqueous-based synthesis processes to minimize the emission of hazardous by-products, hence promoting a more environmentally friendly and secure manufacturing process. Moreover, these green QDs frequently exhibit biodegradability, implying that they can decompose into harmless constituents gradually, so mitigating the ecological consequences in the long run [48]. By using green biomaterial principles in the synthesis of QDs, not only do we support worldwide initiatives to create a circular economy, but we also guarantee the safe and efficient utilization of these advanced materials in various applications, including medical diagnostics and environmental sensing.

3 Nanocomposites in neurodegenerative disorder remediation

Neurological diseases, which are a significant cause of disability and mortality globally, contribute to 12% of all fatalities. Neuroinflammation (INF) is widely recognized as a common feature of various neurological disorders, including PD, AD, and multiple sclerosis (MS), among others. Due to the presence of the BBB, numerous drugs with potential therapeutic effects for neurological diseases are unable to penetrate the brain in sufficient amounts to be effective [49–51]. The discovery of medicines for central nervous system (CNS) illnesses has a lengthy history. However, because of low absorption rates, inadequate concentrations, and the absence of personalized therapy, these medications may have limited efficacy for the majority of patients. Hence, it is imperative to develop distinct therapeutic approaches that effectively target and destroy diseased areas while sparing normal tissue. The CNS undergoes immunological activation in response to viral infections, immune-mediated illnesses, and neurodegenerative diseases [52]. This activation entails the operation of microglia and astrocytes, which are the immune cells residing in the CNS

[53–55]. Furthermore, myeloid cells not only contribute to the inflammatory response but also play a role in regulating neuronal function by facilitating developmental synaptic pruning and plasticity in the healthy brain [56]. The generation of neurotoxic substances such as cytokines and interleukins has been linked to neurodegenerative disorders like AD, MS, PD, and amyotrophic lateral sclerosis, among others.

Although nanomedicines possess exceptional physical and chemical characteristics that offer significant benefits in diagnosing CNS illnesses, there are still unresolved issues regarding potential health risks and the implementation of nanomedicines in clinical surroundings [57]. Nanotechnology offers groundbreaking applications in the diagnosis of brain diseases, leveraging the unique properties of nanoparticles (NPs) to enhance imaging precision and therapeutic targeting. Table 1 shows different types of NPs and their applications in comparison to QDs. Among the most notable are iron-oxide nanoparticles (IONPs), which are extensively used due to their superparamagnetic characteristics, making them highly effective in magnetic resonance imaging (MRI) [58]. IONPs functionalized with molecules such as citric acid and RGD peptides exhibit improved permeability and retention, specifically targeting glioblastomas. These functionalized NPs can cross the BBB, allowing for detailed imaging of brain tumours in both *in vitro* studies with U87-MG glioblastoma cells and *in vivo* models such as BALB/c mice. The integration of IONPs into MRI protocols provides high-contrast images, crucial for the early detection and monitoring of glioblastomas and INF, underscoring their significance in neurodiagnostic applications. Gold nanoparticles (AuNPs) present another innovative approach, particularly effective for their optical and electronic properties that are utilized in various imaging techniques. When conjugated with PEG or antibodies such as anti-CD133, AuNPs enhance the targeting specificity for glioblastomas, facilitating advanced imaging techniques like laser scanning microscopy and X-ray computed tomography (CT) [59]. These conjugated AuNPs provide enhanced signal contrast and enable the identification of tumour margins with greater accuracy, making them invaluable in the pre-surgical planning and real-time monitoring of tumour progression. Studies involving AuNPs have demonstrated promising results *in vitro* with glioblastoma cell lines and in animal models, indicating their potential for clinical translation. Additionally, manganese-based NPs offer distinct advantages due to their paramagnetic properties, which make them suitable for use in MRI [60]. These NPs, when encapsulated in hollow structures or combined with other targeting ligands, improve the imaging of hypoxic regions within brain tumours, aiding in the early detection and treatment planning of glioblastomas [61]. Carbon-based NPs, such as carbon dots, are another

Table 1: An overview of the applications of nanotechnology in diagnosing brain illnesses

NPs	Targeting strategy	Neuroimaging technique	Targeted brain disease	Ref.
Iron oxides	Caffeic acid functionalized	MRI	Glioblastoma	[70]
Iron oxides	Cyclic RGD-covalently coupled IONPs functionalized with phosphonate PEG chains	MRI	Glioblastoma	[71]
Gold	Superparamagnetic IONPs	Microwave	Emergent stroke	[65]
	AuNPs coated with CBP4 peptide and PEG	Laser scanning confocal microscope	Glioblastoma	[67]
Manganese oxide	<i>N</i> -(trimethoxysilylpropyl) ethylene diamine triacetic acid silane and folic acid-conjugated	MRI	Glioblastoma	[68]
MWCNTs	Conjugated with Pittsburgh Compound B and gadolinium	SPECT and CT	AD	[66]
Polysiloxane	AGuIX	MRI	Glioblastoma	[58]
Liposomes	Heptamethine cyanine dye IR780	NIR fluorescence imaging	Glioblastoma	[64]
Liposomes	IONPs and DiR in PEG liposomes functionalized with PGN635 F(ab') ₂ fragments	MRI, NIR optical imaging	Glioblastoma	[57]
Liposomes	Gadolinium-diethylenetriaminepentaacetic acid-loaded PEG-coated liposomes	MRI	Glioblastoma	[61]
Liposomes	QD and doxorubicin-loaded liposomes	MRI	Glioblastoma	[62]
Liposomes	QD and docetaxel-loaded	MRI	Glioblastoma	[59]
Liposomes	PEG- <i>b</i> -poly(L-lysine-DOTA-gadolinium)	MRI	Ischaemia-reperfusion injury	[60]
Nanobodies	Anti-A β and anti-pTau	2PFI	AD	[63]
QDs	Encapsulated in poly(styrene-co-maleic anhydride) and conjugated with PEG	2PFI	AD	[69]

promising category, particularly for their biocompatibility and multifunctionality [62,63]. When conjugated with specific peptides, carbon dots can serve as dual-modality probes for both positron emission tomography (PET) and CT imaging. This dual functionality is crucial for comprehensive brain imaging, as it allows for the simultaneous acquisition of metabolic and structural data, which is especially useful in the diagnosis and monitoring of complex conditions like AD and glioblastoma [64,65]. Liposomal formulations have also emerged as significant players in the realm of nanotechnology-based diagnostics for brain diseases. These formulations can encapsulate various imaging agents, including heptamethine cyanine dye IR780, to enhance near-infrared (NIR) fluorescence imaging of glioblastomas. The use of liposomes ensures targeted delivery and prolonged circulation time, which is pivotal for achieving high-resolution images of brain tumours [66]. Moreover, the versatility of liposomes allows for their adaptation in targeting other neurological conditions, making them a flexible tool in neurodiagnostics. Other NP-based strategies include the use of polysaccharide-based NPs for MRI and CT imaging and micellar systems for the delivery of imaging probes across the BBB [67]. These NPs can be tailored for specific diagnostic applications, ensuring high biocompatibility and minimal toxicity. The incorporation of gadolinium-loaded liposomes and micelles further enhances the imaging capabilities, providing detailed insights into brain pathologies [68]. Overall, the diverse array of nanotechnology-based applications in brain disease diagnostics

underscores the potential of NPs in transforming the field of neuroimaging. From high-resolution MRI to multifunctional PET/CT imaging, these advancements highlight the importance of NPs in achieving precise, non-invasive diagnosis and targeted treatment of brain diseases [69]. The continued development and integration of these technologies hold promise for improving patient outcomes through early detection and personalized treatment strategies.

3.1 Nanotheranostics and its usages in neurodegenerative disorders

The advancements in technology across various fields have clearly showcased their beneficial influence on the advancement of medical research. These breakthroughs have enabled the development of cutting-edge and efficient methods, apparatus, and systems that may address a diverse array of intricate diseases and disorders within the human body. Moreover, the increase in research endeavours in this field has led to the development of a wide range of approaches that can efficiently tackle different diseases [72–74]. Nanotheranostics, as defined by Zhang *et al.*, involves the administration of a nanotheranostic agent through various drug particles. Once the agent reaches the intended area of the body, the medication's outer layer tends to break down, leading to the release of the agents. This facilitates the targeting of specific chemicals or neurons that are responsible for or contribute to the illness [75].

Tripathy *et al.* assert that the treatment is receiving significant interest in the medical sector due to its very aggressive nature and its precise targeting of the damaged location in patients' bodies [76]. Furthermore, it may be customized based on the specific ailment and requirements of each person, resulting in the improved practical implementation of the strategy and offering personalized therapy and medication choices [77]. The therapy or treatment has become viable as a result of recent breakthroughs in chemistry and technology. The application of different metal NPs enables the efficient conversion of electromagnetic waves into medically relevant processes at the nanoscale [78]. This chemical phenomenon is paired with laser technology to enhance the penetration of substances into deeper levels of human tissue, resulting in a simpler and more effective method. Although these advancements appear to greatly enhance the effectiveness of the nanotheranostic process, it is debateable whether the current results are solely derived from laboratory studies and the practical use in living organisms still poses a hurdle [79]. The therapy has undergone testing in various scenarios and has been refined through the use of animal, cell, and human modelling. A range of experiments have been carried out, and the results are outlined below to elucidate the current advancements in the field [80–82].

In nanotheranostics, the diagnostic agents utilized for optical imaging, MRI, nuclear imaging, CT, and radionuclides are QDs or fluorescent dyes, iron oxides, radionuclides, and heavy metals, respectively. Therapeutic agents can take the form of hydrophobic chemical medicines, proteins, peptides, genetic elements, or even diagnostic tools [83]. The main components of a nanotheranostic system are nanocarriers in addition to imaging or diagnostic agents. Drug efficacy is increased with decreased toxicity owing to reduced non-specific biodistribution, and nanocarriers promote pharmacokinetics and improve biodistribution of loaded therapeutic and diagnostic moieties at the target tissues [84,85]. Functionalization of these nanocarriers with biomarkers or other targeting ligands has been identified, enabling target-specific treatments and real-time diagnostic capabilities. Nanocarrier loading increases the stability of therapeutic substances, including tiny hydrophobic compounds, peptide medicines, and oligonucleotides [86]. Radiation therapy, immunotherapy, chemotherapy, and surgery are some of the current options for treating neurological illnesses. Additional contemporary treatment modalities for neurological diseases have recently been investigated, including gene therapy, hyperthermia therapy, and stem cell therapy [87]. However, early diagnosis is essential for achieving effective therapy [88]. The utilization of nanotechnology enables the creation of specialized NPs, which can be employed to boost biomedical capabilities for many chronic diseases. This novel

method is now being adopted for therapy and diagnostics. NPs ranging in size from 1 to 100 nm can readily be linked with various ligands such as pharmaceuticals, nucleic acids, proteins, and enzymes, depending on their surface properties, physical and chemical attributes, efficiency in loading medications, drug release capabilities, and, significantly, their low or nonexistent toxicity as carriers [89]. The use of NPs in disease therapy is not new, and ongoing research is being conducted to comprehend the role of these particles in both treatment and diagnostics. The emergence of NPs in the field of nanoscale drug delivery systems has been highly beneficial. These particles not only provide targeted and enhanced drug delivery but also have the ability to overcome the significant obstacle of the BBB. This is crucial for the development of an ensuring cure for neurodegenerative diseases [90].

3.2 Effect of BBB in the path of drug delivery

While there is a wide range of techniques available to suppress INF, some treatments are more advantageous than others. This review specifically examines the therapeutic potential of targeting cytokines such as interleukin 1 (IL-1) and tumour necrosis factor alpha (TNF α), inflammation-mediated receptors, oxidative stress-related enzymes inducible nitric oxide synthase, peripheral immunity, and specific classes of drugs for the treatment of neurodegenerative disorders by suppressing glial activation (Figure 3).

Despite mounting evidence of INF's critical role, the BBB frequently prevents anti-inflammatory medications from reaching their intended target. The BBB is located anatomically at the surface of the choroid plexus's epithelial cells as well as the endothelial cells of arterioles, capillaries, veins, and other similar structures [91]. Although it serves to shield the brain from harmful substances, the BBB also makes it more difficult for medications to cross. Carriers that have been utilized in studies to aid in the transfer of neuroinflammatory medications over these barriers are also highlighted in this review. There has been a lot of research into potential medicinal alternatives, but thus far, very few have made it into clinical trials. Therefore, to effectively treat neurodegenerative illnesses, it is of utmost relevance to discover medicines that can reduce INF while minimizing negative effects. Drug distribution to the brain is a highly complex task. The BBB maintains the integrity of the brain by regulating the passage of substances in and out of it. Despite the utilization of multiple methods to traverse the BBB, medication delivery to the brain remains less effective compared to other areas of the human body. To overcome this complex barrier, it is

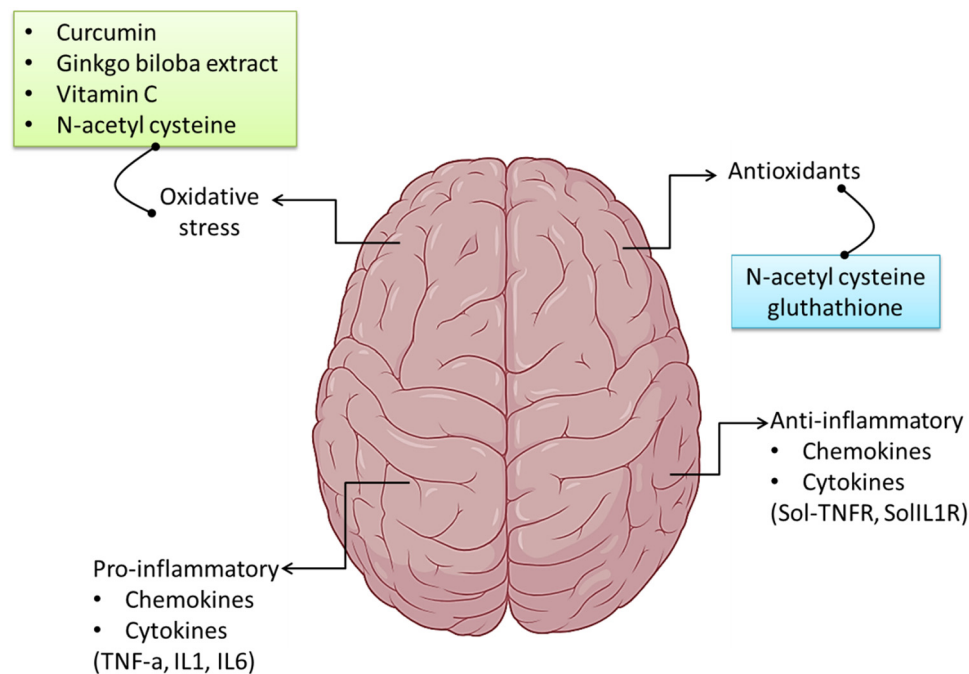


Figure 3: Regulation of the balance between pro-inflammatory and anti-inflammatory responses in the brain, in response to oxidative stress and antioxidants, to maintain homeostasis.

necessary to possess a thorough understanding of the mechanisms and functionalities involved in brain delivery for various components [92]. Additionally, this article discusses the obstacles that exist in drug delivery systems, the tactics that can be used to overcome these obstacles, and various pathways for reaching the brain [93–95]. A wide range of biomolecules, including amino acids, peptides, proteins, antibodies, and carbohydrates, can be utilized for bioconjugation. Bioconjugated vesicles, such as liposomes and niosomes, employ the corresponding receptor or transporter to traverse the BBB. Nitric oxide (NO) is involved in the pathogenesis of neurological diseases. Lithium can modulate NO levels in CNS circumstances by influencing the NMDAR/NO pathway [96]. Low lithium concentrations in relapsing–remitting MS may lead to increased generation of NO, which could potentially affect the progression and treatment of the disease.

It is believed that the BBB is the main obstacle to medication delivery to the brain. Because there are very tight endothelial connections between the brain parenchyma and the microvasculature, the BBB is an impenetrable barrier to the passage of many medications. The composition of the BBB includes a monolayer of endothelial cells, pericytes that are encased within the basal lamina of endothelial cells, and astrocytes that touch the abluminal side of the brain arteries with their end feet. A very resistant paracellular seal is formed when endothelial cells of the

CNS adhere to one another through tight connections; this seal prevents many chemicals and ions from entering the neural tissues [88]. Besides endothelial cells, the astrocytic end feet that surrounds the BBB also control the permeability of the barrier and determine the positioning of transporters. The passage of chemicals, nutrients, and medications across the BBB is facilitated by different transport processes, including passive diffusion, endocytosis, receptor-mediated transcytosis, active transport, and carrier-mediated transport. The transportation processes involve several transport proteins that facilitate the absorption and removal of numerous metabolites and substances across the BBB. Curiously, the BBB is not a literal barrier; it is really dynamic and permits the passage of important nutrients like amino acids, hexoses, proteins, peptides, and ions to support the brain's regular operations, while at the same time preventing harmful chemicals from entering. Furthermore, the existence of efflux pumps, such as P-glycoprotein, expeditiously eliminates any exogenous molecule that manages to evade the BBB. Consequently, only small, fat-soluble molecules, like O_2 or steroid hormones, can easily pass through the BBB with the help of their concentration gradient. Studies have shown that over 99.9% of macromolecules and almost 98% of small molecules with a size larger than 500 Da are unable to cross the BBB. Hence, the distinctive characteristics of the BBB microvasculature control the movement of molecules over the barrier and have a

substantial impact on the transport of drugs to the brain, presenting a difficulty for the efficacy of neural treatments [97]. The utilization of NPs is a medicinal strategy that has attracted considerable interest. The nanomaterials utilized in drug delivery research encompass nanotubes, micelles, nanocapsules, nanoemulsion, liposomes, dendrimers, and a diverse range of organic and inorganic NPs [98,99]. The encapsulation or conjugation of pharmaceuticals to NPs has been found to increase their ability to penetrate the brain, a characteristic that has been widely utilized in numerous research investigations. Nevertheless, NPs are recognized for their ability to trigger INE, neurotoxicity, and cognitive impairment [100]. It is crucial to take into account the potentially harmful consequences that these carriers could have on the body. For instance, zinc oxide NPs can readily enter the brain by many pathways and cause the death of microglial cells by means of ROS activity that is not dependent on NADPH oxidase [101]. The established mechanisms by which chemicals can traverse the BBB include passive diffusion, carrier-mediated transport, and endocytosis facilitated by specific proteins for drug transportation across the BBB (Figure 4).

The utilization of intrinsic transport networks is a significant and unexplored approach in delivering drugs to the brain. The vascular BBB and blood-cerebrospinal fluid barrier are both highly equipped with known transporters. However, it is anticipated that the bulk of BBB transporters remain unidentified. Transporters for numerous peptides and regulatory proteins often have a heterogeneous

distribution, which can be exploited to selectively deliver drugs to specific regions of the brain. For instance, the BBB transporter responsible for transporting IL-1 is highly concentrated in the posterior division of the septum. Similarly, the leptin transporter is mostly found in the arcuate nucleus of the hypothalamus, while the transporter for APP-directed antisense is predominantly located in the hippocampus. The BBB preserves cerebral equilibrium and restricts the infiltration of harmful substances and microorganisms into the brain. Despite its significance, there is limited understanding of the molecular mechanisms that govern the development and operation of this vital barrier. Researchers conducted a study where they devised techniques to purify and analyse the genetic characteristics of endothelial cells from various tissues [102]. By comparing the gene activity of brain endothelial cells with those from the liver and lung, they created a valuable collection of transcripts that are specifically abundant in the endothelial cells responsible for forming the BBB. By doing this comparison, we have discovered new proteins involved in tight junctions, transporters, metabolic enzymes, signalling components, and unidentified transcripts that are more abundant in endothelial cells of the CNS. The investigation has determined that the RXRalpha signalling cascade is particularly abundant at the BBB, suggesting that this route plays a role in regulating this crucial barrier. This dataset is a valuable resource for comprehending CNS endothelial cells and their interaction with neural and haematogenous cells. Leptin, also known as OB protein, is synthesized by adipocytes

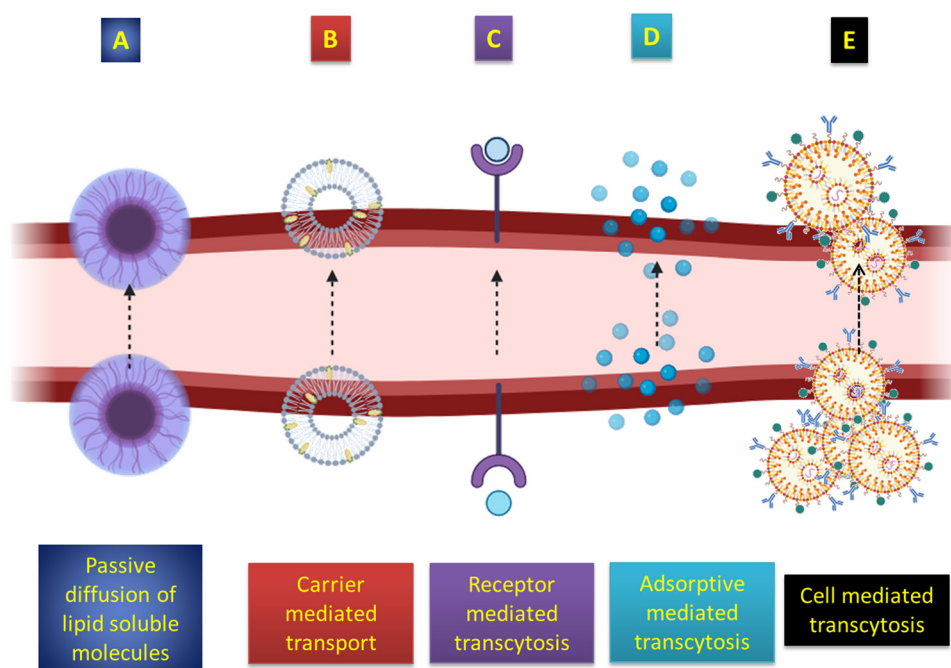


Figure 4: Illustration depicting the ways by which drugs traverse the BBB.

and potentially controls body weight through its influence on the CNS. To access the brain, leptin that is circulating in the body must traverse the BBB. The presence of unlabelled leptin hindered the entry of ^{125}I -leptin in a manner that depended on the dosage. Conversely, unlabelled tyrosine and insulin, which possess transport mechanisms that can reach saturation, did not have any impact. Around 75% of the extravascular ^{125}I -leptin successfully traversed the BBB and entered the brain parenchyma. Uptake was seen at the choroid plexus, arcuate nuclei of the hypothalamus, and the median eminence using autoradiography. No saturable transport was observed exiting the brain [103]. Amyloid β protein ($\text{A}\beta$) is perhaps a causative factor in the development of AD. Prior research has demonstrated that the cognitive impairments that arise in ageing SAMP8 mice, a breed that produces excessive amounts of $\text{A}\beta$, can be reversed with intracerebroventricular injections of an $\text{A}\beta$ antisense phosphorothiolate oligonucleotide (Olg). In this study, we demonstrated that ^{32}P -labelled oligonucleotide (P-Olg) may pass through the BBB of mice without being altered. This transport is facilitated by a specific system called oligonucleotide transport system-1, which operates in a saturable manner [104]. The results of the regression analysis revealed that the blood-to-brain unidirectional inflow rate for P-Olg was determined to be $1.4 \pm 0.39 \mu\text{L/g min}$. Additionally, the capillary depletion experiment demonstrated that P-Olg was able to fully traverse the BBB and reach the brain's parenchymal region. The technique of film autoradiography was employed to illustrate the movement and specific locations of blood-borne radioiodinated IL-1 α and other cytokines into the brain following intravenous delivery [105]. The choroid plexus and the capillary network were labelled with $[^{125}\text{I}]\text{IL-1}\alpha$, $[^{125}\text{I}]\text{IL-1}\beta$, $[^{125}\text{I}]\text{interleukin-1 receptor antagonist (IL-1ra)}$, and $[^{125}\text{I}]\text{TNF}\alpha$ 30 min after being injected into the blood. This indicates that these areas may function as locations for the transit of substances from the blood to the brain. Several medications utilized in the treatment of AD, ranging from clinical applications to preclinical research, have been identified to exploit transport systems. Donepezil, along with other cholinesterase inhibitors, is one of the two classes of medications licenced for treating AD. It is transported through the BBB by an organic cation transporter, most likely the one responsible for transporting choline. A team of researchers studied the choline transport system and investigated how different amine medications affect the choline transporter using a rat brain capillary endothelial cell line (TR-BBB) that can be grown indefinitely in a laboratory setting. The ratio of $[^3\text{H}]\text{choline}$ between the cell and the surrounding medium in TR-BBB cells rose over time. The rate at which $[^3\text{H}]\text{choline}$ is initially absorbed depends on its concentration and can be described by the Michaelis–Menten constant, K_m , which has a value of $26.2 \pm 2.7 \mu\text{M}$. The uptake of $[^3\text{H}]\text{choline}$ into TR-BBB was not

reliant on the presence of sodium ions, although it did depend on the membrane potential [106]. The uptake of $[^3\text{H}]\text{choline}$ was vulnerable to suppression by hemicholinium-3 and tetraethylammonium (TEA), both of which are substrates of organic cation transporters. In addition, the absorption of $[^3\text{H}]\text{choline}$ was hindered in a competitive manner, with inhibition constants (K_i values) of 274, 251, and $180 \mu\text{M}$ when donepezil hydrochloride, tacrine, and α -phenyl-*n*-tert-butyl nitron were present, respectively. A targeted oligophosphorothioate antisense molecule that specifically binds to APP has been found to effectively decrease the amounts of APP in the brain. This leads to an increase in the removal of A-beta from the brain, a reduction in oxidative stress, and an improvement in cognitive function in aged SAMP8 mice [107].

4 Application of QD-based nanocomposites for targeted drug delivery

Investigating the manipulation of materials at the nanoscale is a prominent focus of the current study. Owing to the remarkable advancement of technology, there have been a significant surge in life expectancy and a substantial improvement in the overall quality of life. The advent of nanotechnology has propelled research, particularly in the realm of medical, to unprecedented levels. Given the multitude of benefits associated with nano drug delivery carriers, they can be effectively utilized as vehicles for administering medicines to treat a diverse array of medical conditions. Neurodegenerative disorders in an organism arise from a multitude of factors such as brain injuries, malfunctioning proteins, poisons, and others. However, the causes and origins of many disorders have not yet been definitively established. The primary challenge in treating brain-related conditions lies in the limited permeability of medicinal substances across the BBB. The barrier that separates the blood from the cerebral fluid has a high degree of selective permeability [108]. PD is characterized by the loss of dopaminergic neurons, resulting in a reduction of dopamine levels in the brain. Consequently, the patient's motor function is compromised. Over time, the standard of living declines. Currently, the primary treatment for the initial stages of the condition is the administration of L-DOPA, which serves as the precursor for dopamine [109]. L-DOPA readily crosses the BBB, where it is enzymatically converted to dopamine by L-amino acid decarboxylase or DOPA decarboxylase [110]. In recent

studies, NPs have been found to facilitate drug administration over the BBB and into the CNS, surpassing traditional drug delivery methods. A computational biology technique was used in a study to investigate the activity of α -synuclein, a key factor in the development of PD, in the presence of its inhibitor, cerium oxide (CeO_2) NPs. A computer analysis was performed to examine the effectiveness and level of inhibition caused by the CeO_2 NP on the activity of α -synuclein, using biocompatible metal NPs such as Au NPs and SPIONs. The results indicated that CeO_2 NPs exhibited optimal fitting into the active site of α -synuclein, establishing strong contacts and interactions. Furthermore, they demonstrated potential inhibition of PD in the planned biochemical pathway, as seen by their effect on the L-DOPA medication, which was used as a positive control. Therefore, CeO_2 NPs have been proposed as a promising inhibitor of α -synuclein and can be utilized as a nanodrug to combat PD [111]. In their 2017 study, Yadav *et al.* found that chitosan serves as a medium to facilitate the transport of doxycycline hydrochloride *via* the BBB [112]. The progress of innovative materials for precise and efficient drug delivery is crucial in the field of biomedical research. The research was led to observe the effectiveness of a chitosan/carbon dot (CS/CD)-based nanocomposite as a transporter for the controlled release of dopamine medication. The CDs were produced by carbonizing chitosan and subsequently combined with chitosan (CS) to form a CS/CD matrix. Subsequently, dopamine was enclosed within the matrix to create a dopamine@CS/CD nanocomposite. The study investigated the cytotoxicity of the IC-21 and SH-SY5Y cell lines at different concentrations of the nanocomposite. The findings indicate a cell viability of around 97%. The photoluminescence (PL) property demonstrated the distinctive property of the CDs. Upon excitation at a wavelength of 510 nm, a distinct emission peak was detected at 550 nm, indicating that carbon dots can be effectively utilized as a tracer for bioimaging purposes. The HRTEM images and Raman spectra analysis validate the successful synthesis of carbon dots. Additionally, the particle size is determined to be approximately 3 nm using dynamic light scattering. An *in vitro* analysis was conducted to study the release of the encapsulated medication from the composite material at various pH levels [113]. CDs have garnered significant interest because of their little cytotoxicity and strong biocompatibility, in contrast to metal-based NPs [114]. Furthermore, the synthetic methods used to produce CDs are straightforward, and their significant surface-area-to-volume ratio enables them to possess a substantial drug-loading capacity. Furthermore, owing to their exceptional PL, the distribution of CDs can be monitored in both laboratory-based and living organism-based research [115,116]. Surgical excision is widely acknowledged as a fundamental component in the treatment of malignant

brain tumours. Surgeons encounter significant difficulties in clinical practice when it comes to determining tumour boundaries. This is mostly owing to the infiltrating and diverse characteristics of neoplastic tissues. Contrast-enhanced MRI is widely utilized in clinical settings to accurately identify brain tumours. Regrettably, the commercially accessible (MR) contrast agents exhibit a short-lived circulation lifespan and inadequate penetration across the BBB, significantly impeding their effectiveness in visualizing tumours [117–119]. The study focused on examining the potential of red fluorescent carbonized polymer dots (CPDs) to penetrate the BBB (Figure 5). To summarize, CPDs exhibit extended excitation/emission wavelengths, minimal toxicity, exceptional photostability, and outstanding biocompatibility [116]. Cyclopentadienes demonstrate significant uptake within glioma cells, with the extent of uptake depending on both the duration and dosage of exposure. Once internalized, CPDs mostly accumulate within endolysosomal structures. CPDs have been shown to permeate the BBB in both laboratory and living organism experiments. This finding is significant because it allows for the early detection of brain diseases and the noninvasive imaging of brain tumours, all without causing any harm to the BBB. Moreover, due to the significant disparity between tumour and normal tissue in terms of CPDs, the nanoprobe has the potential to assist in brain tumour removal by providing real-time fluorescence imaging during surgery. MRI was employed to assess the advancement of the tumour 13 days after implantation, confirming the successful formation of the orthotopic glioma model (Figure 5a). Following the administration of CPDs through intravenous injection in the tail, both *in vivo* and *ex vivo* imaging of the brain tissues of rats with C6 glioma were conducted utilizing an *in vivo* optical imaging system. Furthermore, the contour of the brain glioma matched the *ex vivo* imaging shown in Figure 5b and c, providing additional confirmation of the targeting capability of CPDs for brain tumours. Our observation revealed that CPDs were able to quickly cross the BBB and reach the tumour site within 15 min of injection. This suggests that the distribution of CPDs inside the brain may be effectively monitored due to their strong ability to permeate tissues, as indicated by their red fluorescence. The fluorescence intensity of cyclobutane pyrimidine dimers in brain tumours peaked after 60 min and remained strong even at 120 min. This observation aligns well with the *in vitro* BBB penetration studies of CPDs, indicating their great photostability and efficient targeting of gliomas.

To assess the capacity of CDs and CD-based products to traverse the BBB, researchers have established both *in vitro* and *in vivo* models. Lu and colleagues employed

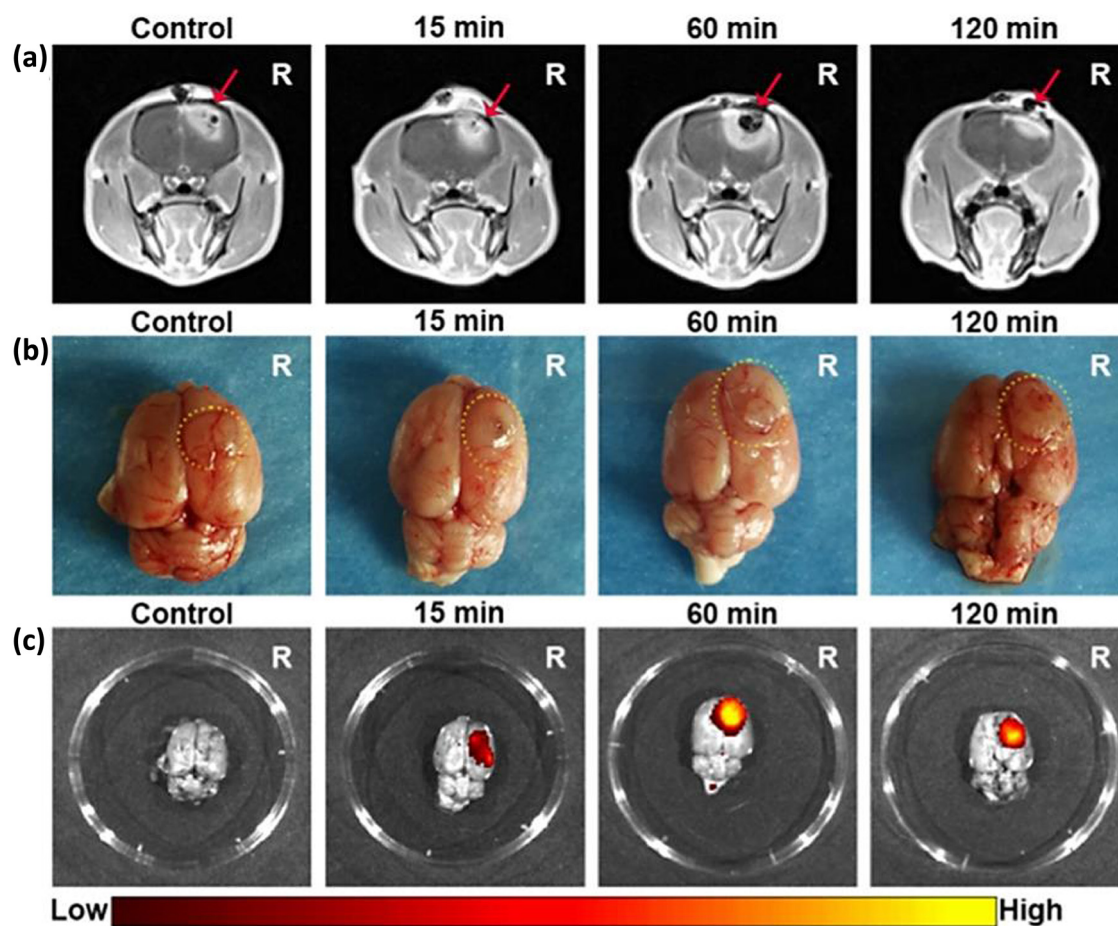


Figure 5: Imaging of glioma-bearing rats using *ex vivo* technique following intravenous injection of CPDs through the tail. (a) MRI was employed to ascertain the presence of tumour formation 13 days after implantation; the tumour tissues were indicated by the red arrows. (b) Images of individual brains displaying tumour tissues are depicted, with the tumour tissues highlighted by dotted circles. (c) Fluorescence imaging of brains *ex vivo* at certain time intervals. Reproduced with permission from Liu *et al.* [116], © 2018 American Chemical Society.

polyethylenimine (PEI) as the starting material to fabricate nitrogen-doped carbon dots (N-CDs) by a single-step solvothermal process. They assessed the N-CDs' capability to traverse the BBB by utilizing an *in vitro* model consisting of rat microvascular endothelial cells and astrocytes [120]. The intense blue PL of N-CDs when exposed to ultraviolet (UV) radiation indicated that N-CDs were transported across the BBB in a manner that depended on their concentration. The utilization of the transwell model in the study of N-CDs serves as a commendable illustration of *in vitro* investigations. The biomimetic model offers the benefits of changeable parameters and restricted changes. However, its fundamental drawback is its limited ability to accurately replicate the BBB in a live animal. Several types of CDs have been tabulated for neurodegenerative disorders in Table 2.

Several peptides, organic compounds, and peptide mimetics have demonstrated promising outcomes in AD by either eliminating aggregation or disrupting the formation of

accumulations in preclinical investigations. Nevertheless, these compounds encounter obstacles such as limited ability to pass across the BBB, reduced stability inside living organisms, decreased effectiveness, and intricate production methods, which ultimately hinder their potential for AD therapy [128]. GQDs are now effective for treating AD because of their capacity to inhibit the development of amyloid plaques and mitigate the cytotoxic effects induced by A β oligomers. This is possible because GQDs can easily pass the BBB due to their tiny size (2–10 nm) and exhibit low cytotoxicity [129]. The hydrophobic interactions between carbon materials and A β 1–42 peptides can limit the formation of amyloid plaques by reducing the negative surface potential. This, in turn, enhances the inhibitory efficacy of QDs [130]. An observable inhibitory impact was found when tramiprosate was covalently linked with GQDs, resulting in a synergistic effect against A β aggregation in AD [121]. Xiao *et al.* developed a novel nanomaterial called GQDs that were

Table 2: Potential uses of QDs in the treatment of neurodegenerative disorders

Type of dots	Disease	Outcomes	Type of study	Ref.
QDs	AD	GQDs combined with tramiprosate exhibit a synergistic effect in inhibiting the buildup of amyloid β .	<i>In vitro</i>	[121]
GQDs	PD	Breaks down α -synuclein proteins into smaller components	<i>In vitro</i>	[122]
GQDs	PD	Anti-aggregation agents hinder the buildup of α -syn and fully formed fibrils, as well as the creation of Lewy bodies. They also prevent neuronal death, the spread of disease, and deficiencies in mitochondrial function	<i>In vivo</i>	[123]
CdTe/CdS/ZnS QDs	PD	Protects against MPP ⁺ -driven α -synuclein fibrillation, cellular damage, and decreases cytotoxicity, apoptosis, and oxidative stress	<i>In vitro</i>	[124]
Glycine-proline-glutamate on QDs	AD	Reduced A β aggregation improves memory and learning capacity, while reducing TNF- α and pro-inflammatory cytokines (e.g. IL-1, IL-6, IL-33, IL-17a)	<i>In vitro</i>	[125]
Branched PEI QDs	AD	Prevents A β plaque development is facilitated by negative targeting and enhanced PL	<i>In vitro</i>	[126]
N-doped CQDs	AD	Prevents amyloid beta protein photooxygenation and Cu ²⁺ -driven aggregation	<i>In vitro</i>	[127]

combined with a neuroprotective peptide called glycine–proline–glutamate (GQDG). They then administered this combined material to mice that were genetically modified to have the APP/PS1 mutation. The *in vitro* experiments, specifically ThT and CD, demonstrated that GQDs and GQDG possess the ability to impede the aggregation of A β 1–42 fibrils. The Morris water maze test was conducted to assess the cognitive abilities and memory capacity of APP/PS1 transgenic mice. The GQDG group exhibited a decrease in the surface area of A β plaque deposition compared to the Tg Ctrl groups. In addition, the freshly formed neural precursor cells and neurons were examined using immunohistochemistry testing. In addition, neurons were labelled with DiI using a gene gun to visualize dendritic spines. The results demonstrated an improvement in learning and memory ability, as well as an increase in the number of dendritic spines. The inflammation factors and amyloid- β (A β) were assessed by suspension array and enzyme-linked immunosorbent assay (ELISA), respectively. The levels of various pro-inflammatory cytokines (IL-1 α , IL-1 β , IL-6, IL-33, IL-17 α , MIP-1 β , and TNF- α) were shown to be lower in the GQDG group as compared to the control group. In contrast, the levels of anti-inflammatory cytokines (IL-4, IL-10) were higher in the GQDG group compared to the control group [131]. *Clitoria ternatea* graphene QDs (ctGQDs) were synthesized using a one-pot microwave-assisted green synthesis procedure by Tak and their team. They specifically focused on extracting the flowers of *Clitoria ternatea* for the purpose of AD therapy. The results indicated that there was a high level of stability. Additionally, the memory acquisition and cognitive function tests, including the radial arm maze and water Morris maze assay, demonstrated a decrease in the time it took to transfer to the hidden platform. The ctGQDs are capable of crossing the BBB due to their smaller size [132]. This enables them to exhibit greater inhibition of the acetylcholinesterase enzyme (Figure 6), reduced levels of lipid peroxidation and nitric oxide, and an increased level of glutathione protein. The positive alterations in the biochemical indicators suggest improved preservation, making them potentially beneficial in the treatment of AD.

To administer the fluorescent QD probes, an anti-A β antibody is coupled with them. These probes are then injected intra-cerebroventricularly into both healthy mice and transgenic mice that carry human APP695swe and APP717 V–F mutations. The fluorescent of A β 1–42 was seen in several locations of APP transgenic mice, such as the hippocampus, cerebral cortex, sagittal septum, and striatum, as illustrated in fluorescence microscopy. Furthermore, *in vivo* imaging demonstrated a decrease in fluorescence intensity in comparison to the APP transgenic animals [133]. Similar to the previous example, CdSe@ZnS QDs were investigated for their potential use as a biosensing carrier in the electrochemical

detection of the ApoE-significant biomarker in AD. Through the utilization of an immune-complex assay that was carried out in a chip with flow mode, the evaluation of ApoE was carried out. Indicating the significance of the tosyl-activated magnetic beads platform as a biomarker in AD, the platform consists of a polydimethylsiloxane-polycarbonate microfluidic chip with integrated screen-printed electrodes. Square wave anodic stripping voltammetry demonstrated that CdSe@ZnS QDs exhibited a limited range limit of detection, resulting in a greater level of accuracy among diluted human plasma samples [134]. The CdSe@ZnS QDs were synthesized by the identical research team to detect apolipoprotein E (ApoE). The sandwich immunocomplex microarray was evaluated using the fluorescent dye Alexa 647 to conduct comparative analyses. The experiment was conducted under comparable conditions, employing the ELISA that specifically targeted ApoE, for the purpose of comparison. The excitation wavelength results demonstrated that QDs are extremely effective biosensing reporters in microarray assays, with a lower limit of detection that is five times more sensitive than Alexa microarrays and seven times more sensitive than ELISA [135].

Spongiform encephalopathy (SE), often known as prion disease, is characterized by the gradual development of brain disease that has a sponge-like structure [136]. Prion disease is a neurodegenerative condition characterized by the formation of cysts or vacuoles, resulting in the replacement of healthy brain tissue with a sponge-like structure [137]. The development of prion disease is rooted in the

accumulation of misfolded prion proteins mostly in the cerebral cortex and cerebellum. Prions are contagious polypeptides found in the cell membrane of specific neurons. They are composed of around 253 amino acids arranged in three α -helix and two β -pleated sheets. The precise roles of prion proteins remain unknown; however, they do have a role in the absorption of Cu from neuronal cells. Mammalian prions possess the capacity to replicate by using regular proteins, resulting in their transformation into the disease-causing variant known as PrP^{Sc} [138]. The misfolded proteins underwent minimal proteolysis, resulting in the creation of tiny, protease-resistant fragments consisting of 142 amino acids. This molecule then polymerizes into amyloid, characterized by two α -helix structures and an increased number of β -strands. The infectious variant prion proteins exhibit a strong attraction to brain activity, leading to their accumulation in neuronal cells and triggering the apoptosis process, ultimately resulting in cell death [139]. Therefore, the brain exhibits a porous structure as a result of the frequent cell death caused by the development of cysts, and the detrimental aggregation of prion proteins on the neurons' membrane leads to the formation of large plaques [140]. The manifestations of prion disease encompass dementia, insomnia, paralysis of the lower limbs, lack of coordination, abnormal sensations, and aberrant conduct. However, the primary clinical presentation of SE is Creutzfeldt–Jakob disease caused by genetic abnormalities in the PRNP gene.

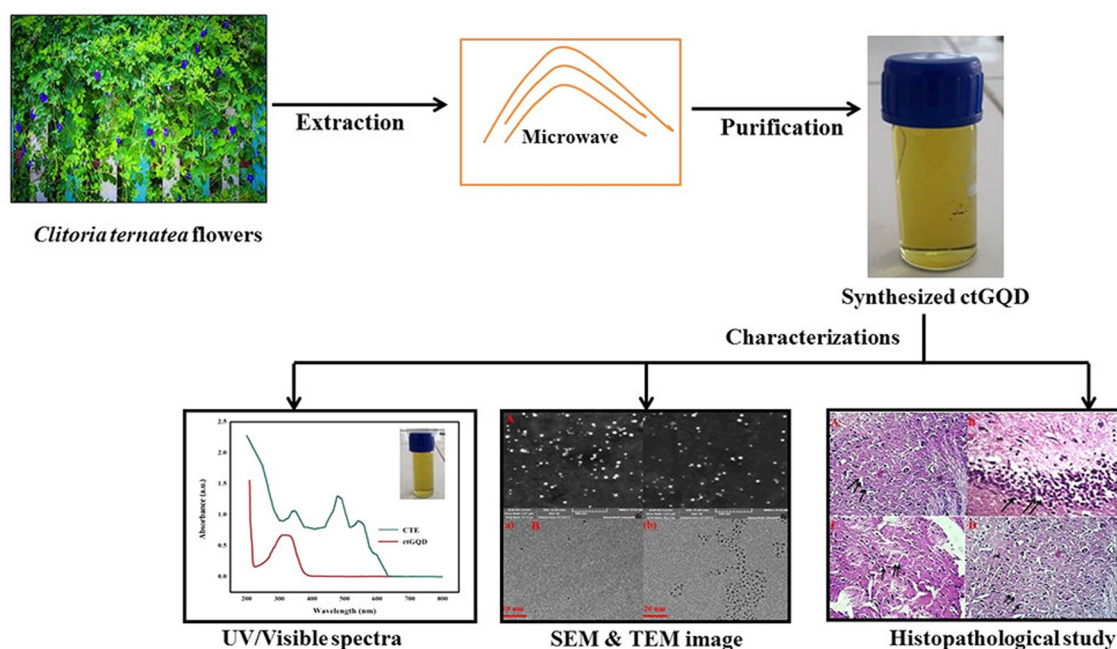


Figure 6: *Clitoria ternatea* was responsible for the synthesis of GQDs, which were then used in the treatment of AD. Reproduced with permission from Tak *et al.* [132], © 2020 American Chemical Society.

5 Neuroimaging applications of surface-engineered QD nanocomposites

Neuroimaging is crucial for the timely detection of several neurological illnesses, offering essential information about the brain's structure and function [141]. The importance of neuroimaging techniques, such as MRI, CT, and PET, cannot be exaggerated in the prompt detection and treatment of neurological diseases [117,142,143]. Neuroimaging has a key benefit in early diagnosis as it may effectively detect structural abnormalities in the brain. Structural imaging modalities such as MRI and CT enable clinicians to observe the intricate details of the brain's anatomy [119]. It is essential to recognize lesions, tumours, or abnormalities that could suggest illnesses such as brain tumours, vascular malformations, or neurodegenerative diseases [144]. Timely identification of these structural alterations allows healthcare practitioners to immediately react, perhaps averting more harm and enhancing patient outcomes [145]. Furthermore, neuroimaging plays a crucial role in the diagnosis of neurological illnesses at an early stage when symptoms may not be detectable from clinical observation alone. Several neurological disorders, including AD and MS, display inconspicuous or vague symptoms during their initial phases [146,147]. Advanced imaging methods, such as functional MRI (fMRI) and PET scans, allow for the evaluation of brain activity and metabolism [148]. By detecting alterations in blood flow, glucose metabolism, or neurotransmitter activity, these methods can reveal irregularities prior to the appearance of clinical symptoms, enabling prompt intervention and control.

For stroke, prompt diagnosis is crucial for optimal therapy. Neuroimaging techniques such as CT and MRI are essential for differentiating between ischaemic and haemorrhagic strokes, assisting doctors in selecting the most suitable treatment measures [149]. The prompt identification of the kind and site of a stroke can have a substantial impact on the selection and timing of therapies, such as thrombolytic therapy or clot retrieval techniques [150]. This, in turn, can result in enhanced results and decreased disability. Moreover, neuroimaging plays a crucial role in enhancing our comprehension of the advancement and pathological aspects of several neurological illnesses. Imaging techniques used in longitudinal research offer useful data on the progression of diseases over time, providing insights into potential biomarkers and targets for therapeutic interventions [151]. This information is extremely valuable for the advancement of new therapies and the improvement of current ones. Neuroimaging is helpful in understanding the intricate connection between

brain structure, function, and mental health in psychiatric diseases. Conditions such as schizophrenia, bipolar disorder, and depression have been linked to distinct brain abnormalities that can be observed by imaging investigations. Timely identification of these alterations in structure and function enables more accurate diagnosis and focused treatment approaches, such as pharmaceutical and psychotherapy therapies [152]. To summarize, the significance of neuroimaging in the early detection of medical conditions cannot be emphasized enough. It significantly transforms the discipline of neurology by offering non-intrusive, comprehensive understanding of the structure and functionality of the brain [153]. Neuroimaging is crucial for promptly diagnosing and treating neurological and psychiatric illnesses, as it allows for the identification of anatomical abnormalities and the detection of minute changes in brain activity [154–156]. With the progress of technology, the possibility of diagnosing medical conditions at an earlier stage and with greater precision is increasing, which brings optimism for enhanced patient outcomes and quality of life. Figure 7 illustrates the currently most frequently utilized noninvasive functional imaging techniques and their spatial and temporal capabilities. It is evident that among these very advanced technologies, fMRI achieves the greatest level of spatial resolution. fMRI is capable of evaluating the entire brain and capturing the hemodynamic processes occurring at the layered and columnar levels of the human cortex. This is achieved by utilizing a high-intensity magnetic field, which operates at a submillimeter level [157]. However, its temporal resolution for viewing the dynamics of neuronal populations is comparatively weaker. Both electroencephalogram and magnetoencephalography are capable of detecting electromagnetic fluctuations at the millisecond level. Nevertheless, their spatial resolution/uncertainty exceeds several millimetres [158]. Most imaging methods lack quantitiveness and thus rely on other data to obtain complementary information. The inclusion of this supplementary data enables the standardization of signals, attainment of absolute measurements, and comparison across different subjects. For instance, the fMRI signal quantifies the activity of neurons through hemodynamic changes resulting from intricate physical and physiological processes. Across other disciplines or regions of the brain, equivalent levels of neural activity can elicit distinct related fMRI findings. Therefore, fMRI data may only be regarded as approximately proportionate to the neural activity. In 2008, Ances conducted experiments that discovered a correlation between cerebral blood flow and fluctuations in fMRI signals in specific brain areas, age groups of patients, and their health conditions. The wide applicability of fMRI results in a heightened sensitivity of the signal it produces [159].

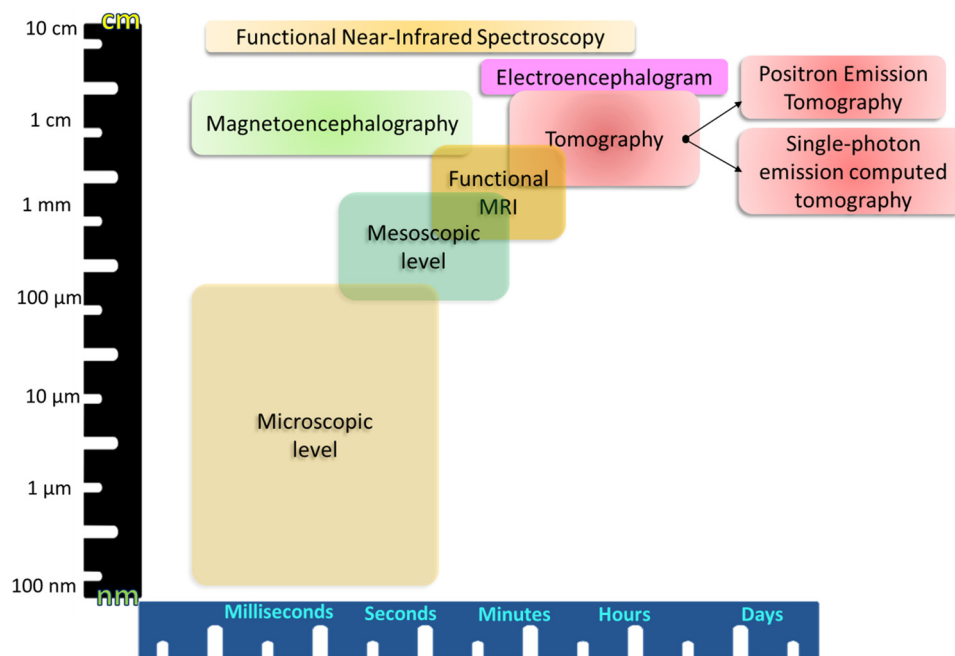


Figure 7: Functional neuroimaging techniques and modalities.

Surface-engineered QD nanocomposites are an innovative advancement in the field of neuroimaging, enabling more advanced and precise investigation of the intricate workings of the brain. QDs, which are nanocrystals made of semiconductors, have unique optical and electronic characteristics that make them very suitable for biomedical purposes [160]. To fully unleash their capabilities, surface engineering is crucial [161]. This involves modifying the outer layer of QDs to enhance their interactions with biological systems. This debate explores the various uses of surface-engineered QD nanocomposites and their ability to greatly impact neuroimaging techniques.

The main attraction of QD nanocomposites is their capacity to adjust their fluorescence, stability, and biocompatibility based on their size [145,162,163]. Their features render them very suitable for neuroimaging applications, where precision and sensitivity are of utmost importance. By altering the surfaces of QDs, scientists are able to precisely adjust their characteristics, thereby improving qualities such as the ability to target specific areas, minimizing harmful effects, and enhancing contrast in imaging. The main benefit provided by surface-engineered QD nanocomposites is the enhancement of contrast and sensitivity in neuroimaging techniques. Conventional contrast agents frequently lack the necessary capability to provide the desired level of resolution for precise imaging of brain structures. Through the modification of the surface characteristics of QDs, scientists can surpass these constraints,

facilitating the identification of small alterations at the cellular and molecular tiers. This increased sensitivity provides opportunities for a deeper comprehension of neuronal activity and the complex networks within the brain. Moreover, the capacity to modify the surface of QD nanocomposites with certain ligands enables precise imaging of brain structures or disease indicators. The focused methodology is crucial for acquiring knowledge about particular areas of interest inside the brain, enabling researchers to comprehend the intricacies of neuronal networks and disease causes. Furthermore, QDs can fulfil a dual function by serving as carriers for medicinal medicines. This distinctive feature allows for the simultaneous visualization and administration of drugs, representing notable progress in the field of neuroimaging where precise treatments are essential. The surface-engineered QD nanocomposites possess a wide range of applications in multimodal imaging, which involves the use of multiple imaging modalities to gain a more thorough understanding of the structure and function of the brain. QD nanocomposites enable researchers to easily integrate data from several sources, including MRI, PET, CT, and optical imaging. By employing a multimodal method, the accuracy and comprehensiveness of the acquired information is improved, resulting in a comprehensive understanding of neurological processes. Although surface-engineered QD nanocomposites show promise in neuroimaging, there are obstacles that need to be overcome for their widespread use. Thorough analysis and mitigation measures are

necessary to address concerns related to long-term biocompatibility, potential toxicity, and regulatory considerations. Ongoing research efforts are focused on optimizing the synthesis and surface modification methods to generate QD nanocomposites that are homogenous and reproducible.

Semiconductor fluorescent QDs are tiny particles that have been modified to exhibit distinct physical characteristics. These attributes make them highly suitable for observing and monitoring molecular events in cells using conventional fluorescence techniques. Existing diagnostic techniques for traumatic brain injury (TBI) which constitutes 15% of all emergency room visits are restricted to neuroimaging approaches. The complexities associated with precise diagnosis and monitoring of TBI have necessitated the development of a straightforward and highly responsive blood test capable of identifying brain-specific biomarkers. A study was conducted to develop a method for detecting S100B, a potential biomarker for TBI. The method involved employing magnetic beads that were attached to antibodies to trap the protein, and QDs that were attached to antibodies for optical detection [164]. The Western blot analysis demonstrates the successful collection and concentration of antigens using magnetic beads. By employing magnetic bead capture and QD detection techniques on serum samples, we demonstrate a broad range of detection and a detection limit that is lower than the clinical cut-off level. Pathak *et al.* quantified the quantity of operative antibodies (*i.e.* antibodies that are physically accessible for effective attachment to target proteins) linked to semiconductor QDs. This is crucial for the analysis of biological data that has been labelled using these techniques (Figure 8). Their investigation revealed substantial variation in the quantity of functional antibodies that are accessible using different conjugation techniques, and these quantities are lower than previously thought. These findings may indicate possible approaches for enhancing the use of QDs in labelling biological samples [165]. The structure consists of three components: a 25 kD light chain, which contains half of the specific antigen binding site for a specific IgG molecule, a 50 kD heavy chain, which contains the other half of the binding site, and a 75 kD partially cleaved chain made up of a heavy chain and a light chain that are connected by an unreduced disulphide bond (Figure 8a). Subsequently, each separate fragment was chemically attached to QDs using an SMCC linkage bond that is resistant to being disrupted by DTT treatment. This is a crucial factor to take into account when analysing the experimental findings that come next. Three potential scenarios for the binding of antibody fragments to QDs can arise: covalent attachment of light chains, covalent attachment of heavy chains, and covalent attachment of partial fragments consisting of heavy and light chains. Among these scenarios, only the last one allows for

further reduction with DTT to remove the light chain fragment from the heavy chains that are still bound to the QDs or to remove heavy chains from light chains that are bound to the QDs. Biotinylated antibodies are modified with four to eight biotin molecules that are randomly bonded to various positions on the entire antibody. This allows the IgG molecules to be linked to QDs, presumably in all feasible spatial configurations (Figure 8c). In contrast to the direct covalent conjugation procedure, the biotin–streptavidin system allows for the complete conjugation of the antibody molecule to the QD. This means that the antibody molecule is not broken down into light chain and heavy chain fragments before attaching.

QDs are extensively employed as fluorescent probes for targeted imaging of cells. Nevertheless, encountering non-specific binding to biological membranes has posed a significant obstacle. A different investigation introduced a novel method to efficiently decrease the occurrence of non-specific binding caused by bovine serum albumin (BSA)-coated QDs in cell targeting [166]. The experimental results demonstrate the successful transfer of hydrophobic QDs from an organic phase to an aqueous phase in the presence of an aqueous solution of BSA under ultrasonication. This method, which uses ultrasonication, is simple, fast, and effective (Figure 9). The stabilization of QDs is primarily accomplished by the presence of several mercapto groups in BSA macromolecules, which act as multidentate ligands. Additionally, the contact between BSA and the fatty ligands attached to the QDs contributes partially to their stabilization through hydrophobic interactions. The presence of amino and carboxyl groups on the surface of QDs enhances their water solubility and also offers sites for the attachment of targeted ligands by conjugation. The QDs covered with BSA, primarily having a hydrodynamic diameter of approximately 18 nm, demonstrate colloidal stability in both acidic and basic environments and display high levels of fluorescence. BSA-coated QDs efficiently decrease nonspecific cellular binding, in contrast to CdTe QDs coated with mercaptopropionic acid (MPA). QDs coated with BSA are additionally modified with cyclic Arg–Gly–Asp (cRGD) peptide. The cell experiments demonstrate the great specificity of the imaging technique for cells expressing integrin $\alpha v \beta 3$.

GQDs are now being utilized for *in vivo* brain labelling. Qian and her colleagues utilized GO NPs with a diameter of 40 nm, which is in line with the size of GQDs [167]. The researchers administered GO-PEG NPs to mice through intravenous injection and used two-photon imaging to monitor how the NPs flowed, distributed, and were cleared in the blood vessels. In addition, the researchers introduced the NPs into the brains of mice that had fluorescent oligodendrocytes through microinjection. The imaging data

obtained using two-photon and three-photon luminescence techniques demonstrated the ability to differentiate GO NPs located at a depth of 300 mm within the brain. A novel variant of carbon dots (CD-Asp) possessing targeted properties for glioma, a kind of brain cancer, was synthesized

utilizing a direct pyrolysis method employing d-glucose and l-aspartic acid as initial substances. The CD-Asp produced in this study demonstrates exceptional biocompatibility and the ability to emit a wide range of colours that can be adjusted. Furthermore, it reveals a notable capacity to specifically

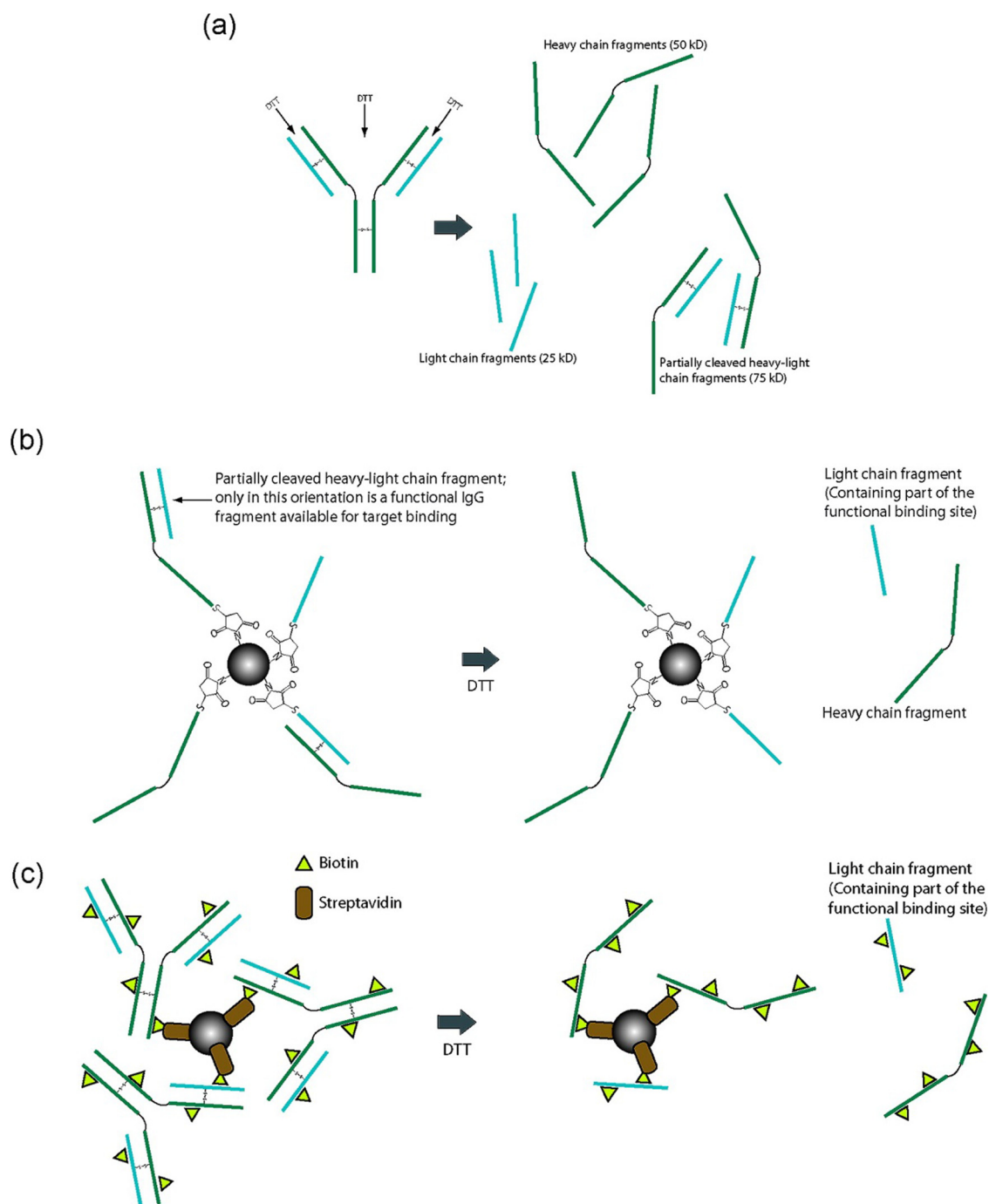


Figure 8: Reducing and conjugating antibodies to QDs. (a) DTT disulphide linkage antibody cleavage sites schematic. DTT reduction can produce light chain, heavy chain, and incompletely cleaved fragments. (b) Direct SMCC covalent antibody-QD conjugation schematic. After the conjugation procedure, DTT reduction creates light chains, which are counted to calculate the average number of functional IgG molecules on QDs. (c) Biotinylated antibodies conjugated to streptavidin-coated QDs schematic. Reproduced with permission from Pathak *et al.* [165], © 2007 American Chemical Society.

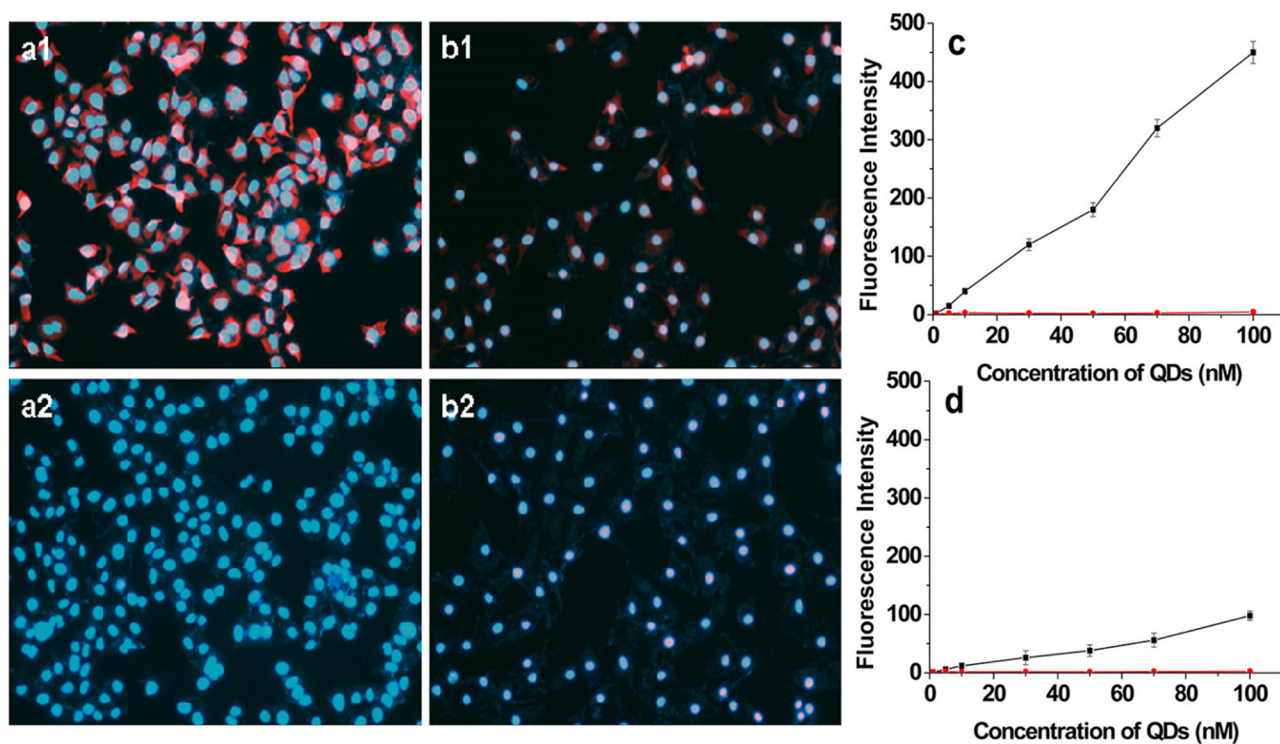


Figure 9: Fluorescent imaging comparison (a and b) and quantitative assessment (c and d) were conducted to assess the nonspecific cellular binding of MPA-coated CdTe QDs (a1, b1, ■) and BSA-coated QDs (a2, b2, ●) on HeLa (a) and 3T3 (b) cells. Reproduced with permission from Zhang *et al.* [166], © 2012 American Chemical Society.

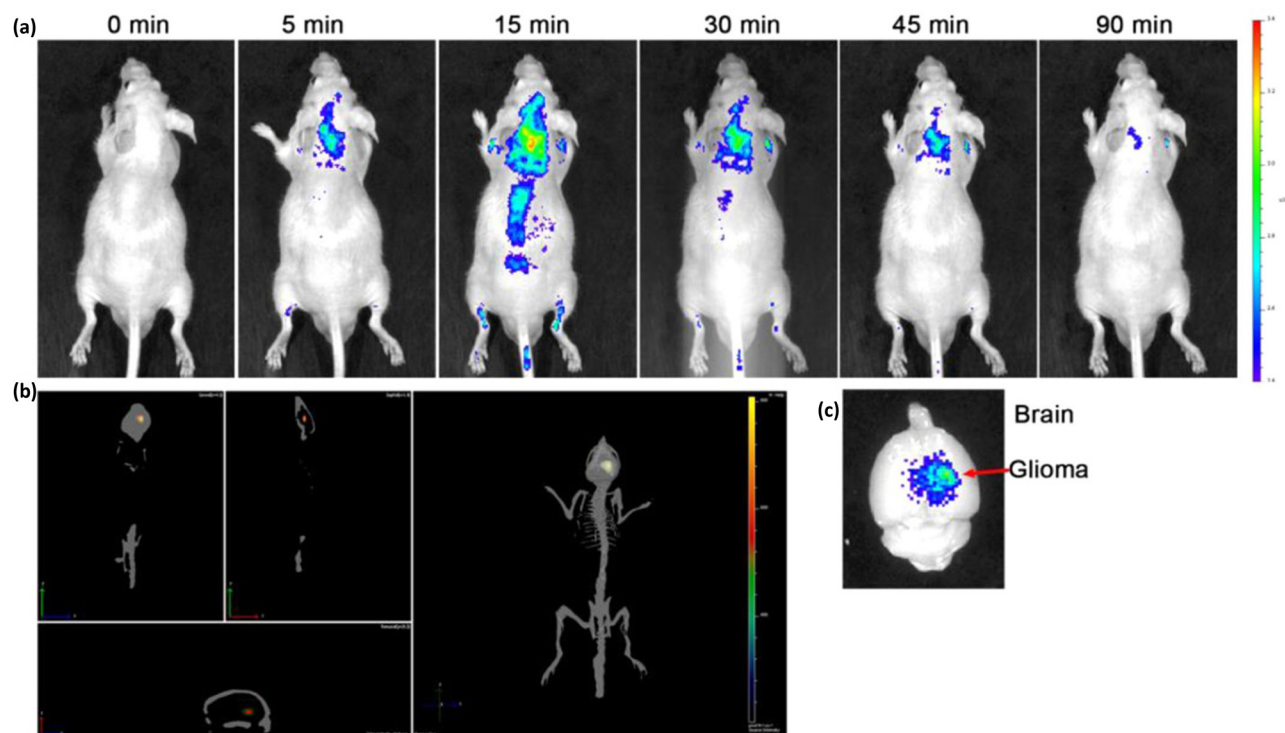


Figure 10: Imaging of glioma-bearing mice was conducted both *in vivo* and *ex vivo* following the administration of CD-Asp *via* intravenous injection into the tail. (a) The temporal distribution of CD-Asp throughout the entire body upon injection. (b) The brain's distribution of CD-Asp 20 min after injection is visualized by three-dimensional reconstruction. (c) Imaging of the brain *ex vivo* 90 min post-injection of CD-Asp. Reproduced with permission from Zheng *et al.* [168], © 2015 American Chemical Society.

target C6 glioma cells, without the need for additional targeting agents. Fluorescence images taken inside a living organism demonstrated a clear and distinct distribution pattern of CD-Asp just 15 min after it was injected into the tail vein (Figure 10). The tumour site exhibited a significantly more intense fluorescent signal compared to the normal brain, suggesting its capacity to easily cross the BBB and accurately target glioma tissue. However, the CDs derived from D-glucose (CD-G), L-aspartic acid (CD-A), or a combination of D-glucose and L-glutamic acid (CD-Glu) do not exhibit significant selectivity for glioma. Thus, CD-Asp has the potential to function as a fluorescent imaging and targeting agent for the noninvasive diagnosis of glioma [168].

6 Biocompatibility and toxicity

QDs have a wide range of applications in fields such as sensor technology, bio-imaging, drug delivery, and therapeutics. One significant concern regarding the utilization of QDs in biological applications revolves around their potential toxicity. Each individual QD possesses its own unique physicochemical property that plays a crucial role in determining its potential toxicity. The toxicity of QDs is influenced by various factors: (i) size, (ii) compounds utilized in the fabrication process, (iii) doses, (iv) environmental condition, (v) material used for capping, and (vi) administration route of QDs [169].

Carbon, silicon, and group I–III–VI₂ materials are utilized for biological applications due to their non-toxic nature. The initial discovery of CQDs was made within a single-walled carbon nanotube. These NPs are harmless and simple to create. They are well-suited for biological and biomedical applications because of their aqueous solubility. The Group I–III–VI₂ elements, such as Cu, Al, Ag, S, Se, and Te, possess excellent PL characteristics and have a lower level of toxicity [169]. One of the most commonly used QDs in various applications is CdSe. Cadmium exhibits high levels of toxicity and tends to accumulate in the spleen without undergoing degradation. Recent findings indicate that the use of cadmium-based QDs can lead to inflammation in the lungs. Additionally, the oxidation of cadmium QDs produces a reduced form of cadmium, which ultimately leads to cell death. In addition to cadmium-based QDs, the toxicity assessment of various other QDs, including Ag₂Se QDs, CuInS₂@ZnS, InP QDs, and hybrid QDs of carbon and CdSe@ZnS are also reported. Every type of QDs possesses unique benefits. Cadmium-based QDs exhibit a wide range of UV excitation, emit a narrow spectrum of light, and have high PL. In contrast, cadmium-free QDs have

minimal toxicity. Multiple experiments have consistently demonstrated that the toxicity of QDs is directly influenced by the dosage, regardless of their composition. Therefore, surface modification plays a crucial role in decreasing toxicity while enhancing the biocompatibility, stability, and specificity of QDs. Thus, the method of modifying QDs with inorganic shells (such as CdSe@ZnS, CdSe@SiO₂), polymers, and bio- or natural macromolecules is advantageous [170]. Nurunnabi *et al.* conducted a study on the *in vivo* dispersion and potential toxicity of carboxylated photoluminescent GQDs. The carboxylated photoluminescent GQDs were tested on KB, MDA-MB231, A549 cancer cells, and MDCK normal cell line as *in vitro* cell culture models to investigate potential negative impacts [171]. The carboxylated GQDs are advantageous due to their enhanced ability to dissolve in water. The carboxylated GQDs were effectively internalized by all cancer cells. There were no signs of immediate harm or physical changes observed in either system at the amounts of exposure that were examined. The utilization of histological analysis to detect the carboxylated GQD NPs enables a comprehensive microscopic evaluation and histological assessment of tissue interactions. The findings visually depict the presence of inflammation or lesions resulting from the intravenous administration of GQD NPs. Upon histological examination of animal tissues, no evident histopathological abnormalities or lesions were detected in the heart, kidney, and spleen (Figure 11). The histological staining images of these organs exhibited identical characteristics to those of the control animals. The histological investigation revealed no significant signs of toxicity; however, considerable pathological alterations were identified in the liver and lung 21 days after administering carboxylated GQD NPs at a higher dosage of 10 mg/kg.

Tabish *et al.* conducted a study where they administered high doses of GQDs to rats for a period of 4 weeks [172]. They found that there was only a small amount of toxicity observed in the rats during this time. Additionally, they were able to confirm that the GQDs increased the production of singlet oxygen and other reactive oxygen species. Rat tests assessing *in vivo* toxicity reveal that our GQDs exhibit negligible dark toxicity, a crucial characteristic of a photosensitizer intended for future application in PDT. Boron-doped GQDs are synthesized using a one-pot acid-free microwave method, where graphene oxide is used as the carbon source and borax is used as the boron source [173]. The conventional MTT assay indicates that the B-GQDs exhibit minimal cytotoxicity and favourable biocompatibility. At a concentration of 4.0 mg/mL, the B-GQDs achieve a cell viability of 87%. B-GQDs are practically applied in bio-analysis through the use of bio-imaging to visualize HeLa cells. Semiconductor QDs have the potential to greatly enhance the effectiveness of biomedical NIR

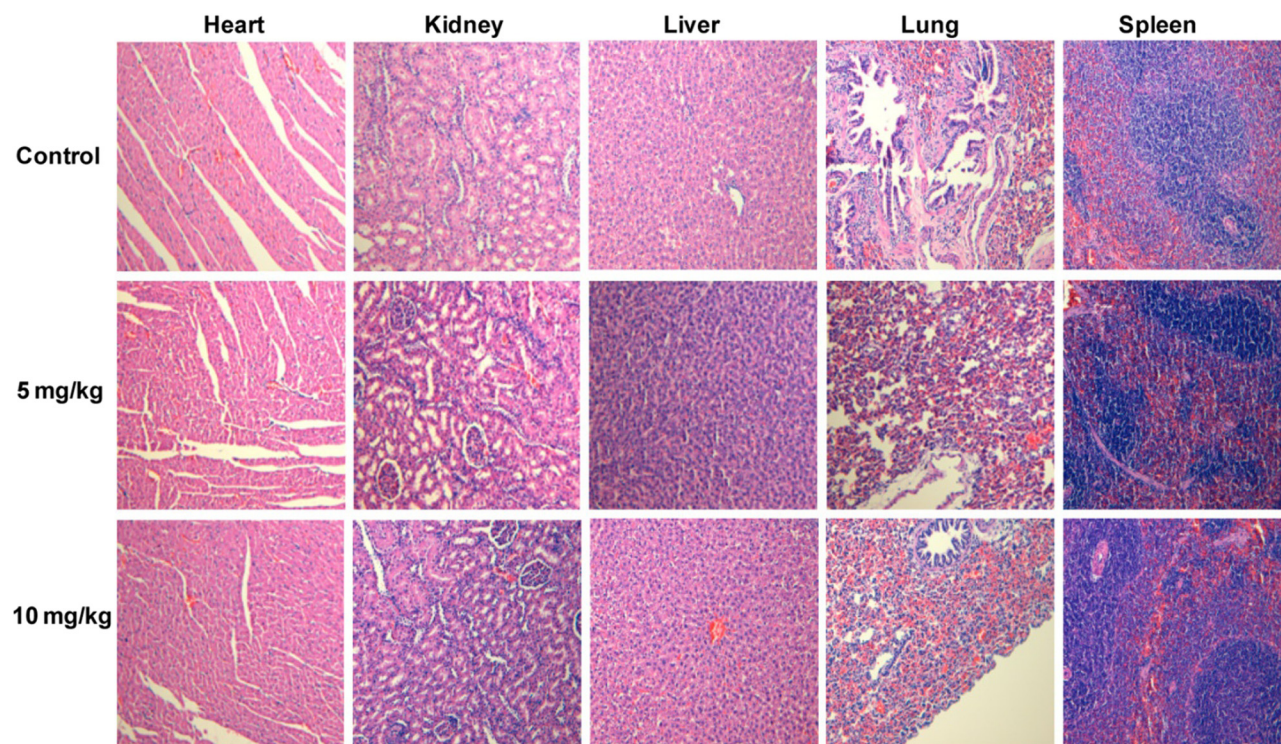


Figure 11: Histological examinations of mice's major organs 22 days after GQD intravenous injection. No inflammation or lesions were seen in the photos. Tissues of 5 and 10 mg/kg GQD-treated mice are identical to saline-treated mice. Photos were taken at 160 \times magnification with haematoxylin and eosin staining. Reproduced with permission from Nurunnabi *et al.* [171], © 2013 American Chemical Society.

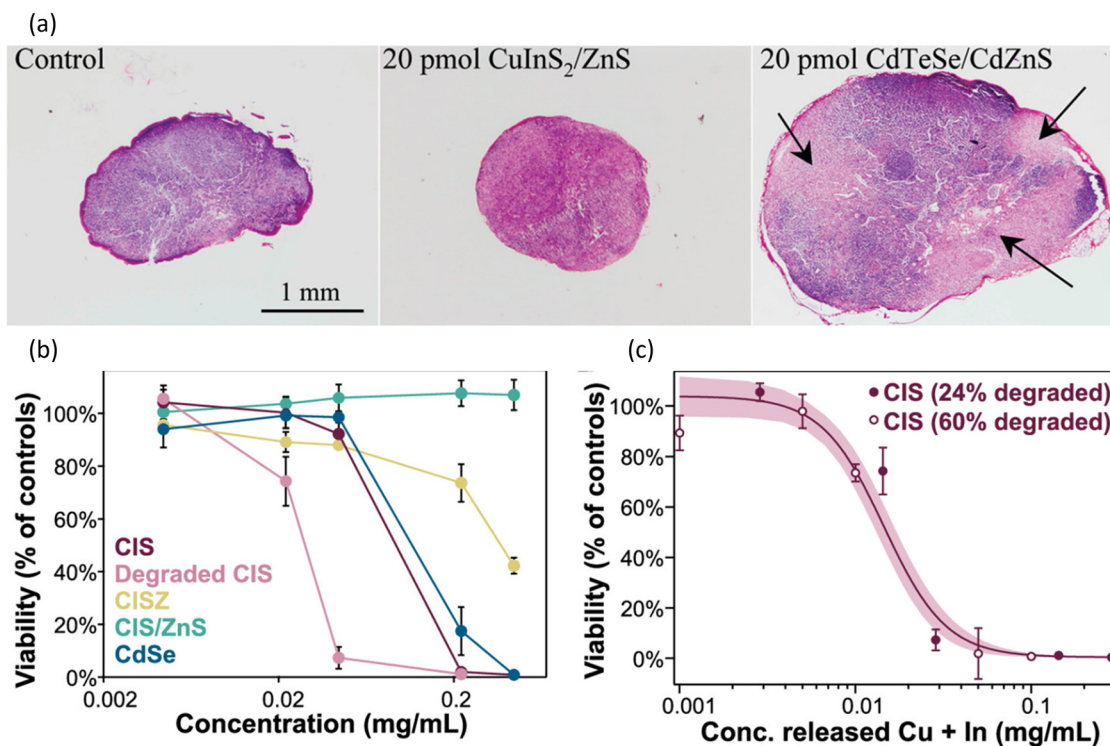


Figure 12: (a) RALN histological sections resected 7 days after injection for animals injected with saline buffer (control), 20 pmol CuInS₂/ZnS QDs, and 20 pmol CdTeSe/CdZnS QDs. Light regions with black arrows suggest inflammation. The scale bar is 1 mm. Reproduced with permission from Pons *et al.* [174], © 2010 American Chemical Society. Toxicity test *in vitro* of (b) QD-treated HepG2 viability after 24 h, $n = 4$ wells per dosage. (c) Dose-response curve from viability testing for two degradation levels fit a 4-parameter Hill equation; shaded region shows 95% confidence interval. Reproduced with permission from Kays *et al.* [175], © 2020 American Chemical Society.

imaging. This is because they can offer fluorescent probes that are both brighter and more resistant to fading compared to traditional organic dyes [174]. The influence of QD composition on the RLTLN is consistent, with injections of CuInS₂/ZnS up to 100 pmol not causing significant inflammation, while an injection of 10 pmol of CdTeSe/CdZnS leads to a significant increase in RLTLN weight compared to the control (3.43 ± 0.61 mg vs 2.33 ± 0.41 mg; $p < 0.05$). Figure 12a displays histological sections of RALNs that were dissected 7 days after injection. The findings from this investigation conducted in a living organism prompted a subsequent examination of cytotoxicity conducted in a controlled laboratory setting. To gain a deeper understanding of the mechanism behind CIS toxicity, we conducted measurements to assess the effects of CIS, partially degraded CIS, CISZ, CIS/ZnS, and CdSe on the HepG2 human liver cancer cell line (Figure 12b and c). The cells were cultured in media containing QDs for a duration of 24 h. Following this, the media was removed, the wells were rinsed with phosphate-buffered saline, and the ATP levels were quantified using a conventional viability assay.

The stability, *in vivo* degradation, and prevention of toxicity of QDs can be influenced by their coating. Group III-IV QDs are commonly utilized in optical probe and biosensor applications due to their reduced toxicity. To reduce the toxicity of QDs, biocompatible functionalization can be adopted. In this approach, the use of (i) mercapto group and (ii) encapsulation in phospholipid micelles, which retain optical properties while causing no surface modifications, are employed to mitigate the harmful effects of the QDs. Other methods include QD conjugation with antibodies [176–178].

7 Challenges and future directions

QD nanocomposites that have been modified on the surface are an emerging area of research in the domains of treating neurodegenerative disorders and neuroimaging. They have the potential to greatly transform our approach to these complicated challenges. Nevertheless, there are other significant obstacles that need to be overcome to fully exploit the capabilities of these nanocomposites for therapeutic and diagnostic applications. The primary difficulty is the urgent requirement for thorough investigations on the biocompatibility and probable toxicity. An in-depth analysis of the long-term impact of surface-engineered QD nanocomposites on cellular and organismal health is required due to the complex interactions between these materials and biological systems. Ensuring the safe and effective use of these nanocomposites in clinical applications requires addressing concerns regarding biocompatibility.

An important challenge in using surface-engineered QD nanocomposites for treating neurodegenerative disorders is the need to effectively cross the BBB. Although there have been improvements in surface changes intended to improve the accuracy of targeting, successfully penetrating the BBB is still a difficult task. It is essential to overcome this obstacle to ensure that therapeutic QD nanocomposites can accurately and efficiently reach their designated neuronal targets. Current research efforts are focused on developing strategies to increase the permeability of the BBB without causing damage to neural tissues. The aim is to fully utilize the capabilities of QD nanocomposites for delivering drugs specifically to the brain.

Furthermore, the transition of surface-engineered QD nanocomposites from laboratory testing to practical use requires thorough verification of their effectiveness and safety characteristics. Establishing standardized techniques for the synthesis, characterization, and functionalization of these nanocomposites is crucial to guarantee uniformity and repeatability in various research and clinical environments. Developing rigorous procedures would enhance the dependability of findings and streamline the comparison of results across research, ultimately accelerating the practical application of QD nanocomposites for the treatment of neurodegenerative disorders and neuroimaging purposes. Within the field of neuroimaging, there are ongoing difficulties in enhancing the imaging capabilities of QD nanocomposites. To obtain images with high resolution and little background noise, it is necessary to continuously improve the synthesis and surface engineering procedures. Achieving a harmonious equilibrium between enhanced contrast and sensitivity, while also minimizing any possible cytotoxic consequences, continues to be a challenging endeavour. Researchers are currently investigating novel methods to optimize the characteristics of QDs, which can lead to improved imaging techniques. These advanced imaging modalities have the potential to offer unprecedented understanding of the intricate details of neuronal structures and functions.

To summarize, whereas surface-engineered QD nanocomposites show great promise in tackling the difficulties of treating neurodegenerative disorders and improving neuroimaging methods, there are still significant obstacles that need to be overcome. To fully unlock the therapeutic and diagnostic capabilities of these nanocomposites, it is essential to address concerns related to biocompatibility, improve the ability to penetrate the BBB, and establish standardized techniques for the synthesis and functionalization processes. Future endeavours entail the collaboration of several fields of study and ongoing creativity to address these obstacles and facilitate the ground-breaking use of surface-engineered QDs nanocomposites in neuroscience and clinical practice.

Table 3: Different types of NPs and their comparison with QDs

Characteristics	QDs	Lipid-based NPs	Polymeric NPs	IONPs	AuNPs	Ref.
Optical properties	Tuneable fluorescence	Variable	Limited	Contrast agent for MRI	Unique optical properties	[181]
Surface engineering	Highly customizable	Limited adaptability	Tailored for drug release	Variable	Surface functionalization	[182]
Biocompatibility	Concerns; ongoing research	Usually high	Generally high	Generally high	Generally high	[183]
BBB penetration	Challenging	May face challenges	May face challenges	Limited	Challenging	[184]
Drug delivery capability	Yes, with surface engineering	Yes	Yes	Limited	Yes	[185]
Imaging capabilities	High-resolution imaging	Inadequate	Limited	MRI contrast agent	Imaging and therapy	[186]
Targeting specificity	Feasible through modification	Achievable	Achievable	Achievable	Attainable	[187]
Clinical translation	Challenges in biocompatibility	Established in some cases	Ongoing research	Widely used	Escalating applications	[188]

8 Comparative analysis with other NPs and practical trials

Within the field of addressing neurodegenerative disorders and studying brain imaging, many methods that involve NPs demonstrate unique properties, along with their own benefits and difficulties. QDs possess adjustable fluorescence and adaptable surface engineering, making them an exceptional choice for combining imaging and drug delivery functionalities. Ongoing research endeavours to fully use the potential of QDs for simultaneous therapeutic and diagnostic purposes, despite concerns over their biocompatibility and ability to penetrate the BBB. Lipid-based NPs, known for their exceptional biocompatibility, are highly effective in delivering drugs [179]. However, they may encounter challenges in terms of their imaging capabilities. Polymeric NPs, which possess customized drug release characteristics, offer a well-balanced method but may face difficulties in producing high-resolution imaging [180]. IONPs are efficient in enhancing the visibility of MRI images, but their potential for therapeutic use is restricted. AuNPs, possessing distinct optical and therapeutic characteristics, exhibit potential in the integration of imaging and therapy. Every form of NP possesses distinct advantages and disadvantages, which must be carefully evaluated according to the specific needs of investigations on neurodegenerative disorders and neuroimaging applications. The continuous progress in surface engineering and biocompatibility plays a crucial role in determining the future of NP-based methods for comprehensive solutions in neuroscience [26]. Table 3 sums up the contemporary NPs and how the QDs are distinguishable among them.

The application of surface-engineered QDs in the treatment of neurodegenerative illnesses is a unique and disruptive method that has potential benefits in both diagnosis and treatment. QDs, such as the Quantum Dot 800 ITK™ and CdSe/ZnS core-shell QDs, have unique optical and electronic characteristics that make them very suitable for neuroimaging [189]. They have unmatched sensitivity and specificity in detecting molecular-level pathological alterations, delivering extraordinary precision. The QDs that have been modified on their surface can be chemically modified with different biomolecules, which improves their ability to interact with living organisms and allows them to be delivered specifically to certain neuronal regions. This focused strategy shows potential in reducing the advancement of conditions such as Alzheimer's, Parkinson's, and Huntington's illnesses [190]. Although QDs have the potential for clinical translation in the treatment of neurodegenerative disorders, their progress in this area is still in the

early stages. Multiple preclinical studies have shown evidence of the effectiveness of nanocomposites based on QDs in animal models. These studies have shown notable enhancements in neuronal function and a decrease in illness indicators. In preclinical backgrounds, *in vivo* therapeutics' imaging agents based on QDs have played a crucial role [191]. Nevertheless, there is a scarcity of human clinical studies, as the majority of research is primarily concerned with examining safety profiles and biodistribution. Thermo Fisher Scientific's Qdot® Nanocrystals, an FDA-approved product, has been used in laboratory settings to identify biomolecules [192]. This demonstrates the regulatory process for these sophisticated materials. The current clinical studies and research endeavours are focused on addressing the issues pertaining to the toxicity and long-term stability of QDs, which are crucial for their extensive use in clinical environments [193]. The incorporation of QDs into therapeutic approaches for neurodegenerative illnesses not only signifies the beginning of a new era in their treatment but also opens up possibilities for cutting-edge neuroimaging methods that have the potential to transform early detection and tracking of these incapacitating disorders.

9 Conclusion

To summarize the main discoveries of this extensive review paper, the investigation of surface-engineered QD nanocomposites for the treatment of neurodegenerative disorders and neuroimaging shows an area full of potential and optimism. QDs possess inherent properties, including adjustable fluorescence and the capability for meticulous surface modification, which make them adaptable instruments suitable for specific drug transportation and detailed imaging within the complex structure of the nervous system. The research synthesis examines the progress and difficulties related to surface-engineered QD nanocomposites. The unique optical properties and tailored surface functionalities of these materials offer significant potential for both therapeutic interventions and precise neuroimaging. Nevertheless, it is crucial to carefully tackle notable obstacles such as biocompatibility, potential toxicity, and efficient permeation through the BBB. The comprehensive assessment underscores the substantial potential of surface-engineered QD nanocomposites to enhance our understanding of neurodegenerative diseases and advance neuroimaging techniques. The landscape is undergoing gradual transformation through ongoing efforts in surface modification techniques, biocompatibility research, and the development of standardized protocols, despite the challenges encountered. The

integration of nanotechnology, neurobiology, and medical imaging has resulted in the rise of surface-engineered QD nanocomposites as frontrunners in the advancement of innovative remedies for brain well-being. To summarize, this research predicts that surface-engineered QD nanocomposites will have a crucial role in understanding the intricacies of neurodegenerative illnesses and advancing neuroimaging capabilities. The ongoing research on nanocomposites shows great potential for their incorporation into clinical practice. This holds promise for improving the diagnosis and treatment of neurological illnesses, which is a difficult area to address.

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