HHS Public Access

Author manuscript

Curr Med Chem. Author manuscript; available in PMC 2024 August 20.

Published in final edited form as:

Curr Med Chem. 2023 ; 30(3): 255–270. doi:10.2174/0929867329666220328125206.

Nanotechnology: A Promising Targeted Drug Delivery System for Brain Tumours and Alzheimer's Disease

Aziz Unnisa[1], **Nigel H. Greig**[2], **Mohammad A. Kamal**[3,4,5,6,*]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Hail, Hail, KSA

[2]Drug Design & Development Section, Translational Gerontology Branch, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA

[3]Institutes for Systems Genetics, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China

[4]King Fahd Medical Research Center, King Abdulaziz University, Jeddah 21589, Saudi Arabia

[5]Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka, Bangladesh

[6]Novel Global Community Educational Foundation, Enzymoics, 7 Peterlee Place, Hebersham, NSW 2770, Australia

Abstract

Nanotechnology is the process of modulating shape and size at the nanoscale to design and manufacture structures, devices, and systems. Nanotechnology's prospective breakthroughs are incredible, and some cannot even be comprehended right now. The blood-brain barrier, which is a prominent physiological barrier in the brain, limits the adequate elimination of malignant cells by changing the concentration of therapeutic agents at the target tissue. Nanotechnology has sparked interest in recent years as a way to solve these issues and improve drug delivery. Inorganic and organic nanomaterials have been found to be beneficial for bioimaging approaches and controlled drug delivery systems. Brain cancer (BC) and Alzheimer's disease (AD) are two of the prominent disorders of the brain. Even though the pathophysiology and pathways for both disorders are different, nanotechnology with common features can deliver drugs over the BBB, advancing the treatment of both disorders. This innovative technology could provide a foundation for combining diagnostics, treatments, and delivery of targeted drugs to the tumour site, further supervising the response and designing and delivering materials by employing atomic and molecular elements. There is currently limited treatment for Alzheimer's disease, and reversing further progression is difficult. Recently, various nanocarriers have been investigated to improve the bioavailability and efficacy of many AD treatment drugs. Nanotechnology-assisted drugs can penetrate the BBB and reach the target tissue. However, further research is required in this field to ensure the safety

*Address correspondence to this author at the Enzymoics, 7 Peterlee place, Hebersham, NSW 2770, Australia; prof.ma.kamal@gmail.com.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

and efficacy of drug-loaded nanoparticles. The application of nanotechnology in the diagnosis and treatment of brain tumours and Alzheimer's disease is briefly discussed in this review.

Keywords

Nanotechnology; brain tumour; Alzheimer's disease; nanoparticles; blood-brain barrier; drug delivery

1. INTRODUCTION

Nanotechnology is the branch of science and engineering, which involves the design, characterization, development, and utilization of structures or devices that have the smallest functional organization, at least one dimension of which is of nanometer scale. Both interacting groups of molecules and individual molecules with bulk macroscopic materials or devices are significant at this scale because they influence the basic molecular structure, enabling them to monitor macroscopic chemical and physical properties. Nanotechnology has sparked interest recently as a way to solve challenges in gene and therapeutic drug delivery [1].

Brain cancer (BC) is the most challenging tumour to diagnose and treat, as it is complicated to get imaging and targeted drugs pass the blood-brain barrier (BBB) and enter the brain. Antineoplastic agents, like loperamide and doxorubicin, coupled with nanomaterials have proven to pass through the BBB and get delivered to the target site at the desired therapeutic concentration. The application of nanomaterials to attack the vascular endothelial growth factor (VEGF) receptor and cell adhesive molecules, such as cadherins, selectins, and integrins, is a novel strategy to limit the condition from further worsening [2].

Nanomaterials have been used to successfully design anti-cancer agents, such as doxorubicin, paclitaxel, dexamethasone, and 5-fluorouracil. *in vitro* delivery of RNAi has also been achieved with quantum dots, chitosan, Polylactic/glycolic acid (PLGA), as well as PLGA-based nanoparticles [2].

Alzheimer's disease (AD), a serious neurodegenerative disorder, is by far the most common type of dementia in people above 65 years of age. It is associated with progressive loss of memory and has two significant characteristics in the brain. This comprises extracellular amyloid-(A) peptide deposition (amyloid plaques) and intracellular hyperphosphorylated protein neurofibrillary tangles of τ protein [3]. The BBB is one of the most significant impediments to the development of new therapeutic agents and biological products for the central nervous system (CNS). Therapeutic agents, even most small compounds, do not usually pass through the BBB. Nanotechnology-based techniques have grown in prominence because some of them have the potential to overcome the obstacles to the BBB passage. Diverse forms of polymeric, lipidic, inorganic, as well as other nanoparticles (NPs) for controlled drug delivery and liberation in several CNS disorders, are some of the examples of such techniques [4].

AD and BC are two major diseases of the brain. Though these two diseases affect millions of people every year, truly effective drug treatments are not available. Although both have different pathologies and pathways, nanotechnology with common elements can be used for drugs delivery through the BBB, and thus can help in the development of treatment therapies for both diseases [5]. Hence, the present review focuses on the utilization of nanotechnology for diagnosing and treating brain cancer and Alzheimer's disease.

2. DRUGS AND BRAIN TUMOR TREATMENT BARRIERS

2.1. Blood-Brain Barrier

Most chemical compounds and circulating cells are prevented from passing the BBB, which is built by a complex combination of pericytes, endothelial cells, perivascular mast cells, and astrocytes. The endothelial cells of the brain capillary, which are interlinked by intact junctions, are primarily responsible for the BBB's tightness. The BBB is not simply a mechanical barrier but a biological entity that includes active metabolism and carrier-mediated transports [6].

The uptake of most drugs and pharmaceuticals by the brain is impeded by the BBB, except for small hydrophilic molecules with a mass less than 150 Da and highly hydrophobic elements with a mass less than 400–600 Da that can permeate through the membrane by passive diffusion [7]. Opiates, SSRIs, anxiolytics, and antipsychotics are among the drugs that are permeable to the BBB, however, most antibiotics and antitumoral agents are impermeable. A variety of techniques have been utilized to make the drugs pass through the BBB. These strategies include chemical alterations of drugs to utilize physiological carrier-mediated transports, invasive techniques, and the use of the so-called "Trojan horse" technique, which pairs impermeable drugs to molecules that can pass through the barrier using transport systems mediated by receptors [8].

New routes of drug administration that can bypass the BBB and reach the brain (*e.g.*, intranasal) have been intensively researched, but they are restricted by the olfactory bulb's limited surface of adsorption, which is small in comparison with the BBB, thereby minimizing the possibility of entering the brain with relevant quantities of drugs [8].

2.2. Other Brain Tumor Treatment Barriers

The brain tumour-cell barrier (BTB, a barrier developed due to the efflux activity of tumour cells) is the extra barrier that curtails the entrance of systemically administered drugs into the brain. Other issues related to the effective treatment of brain tumours include myelosuppression resulting from dose-limiting toxicity and the development of drug resistance by tumour cells [9].

3. DIFFERENT TYPES OF NANOPARTICLES FOR BRAIN DRUG DELIVERY

3.1. Lipid-Based Nanoparticles

3.1.1. Liposomes—Liposomes are composed of one or more vesicular bilayers (lamellae) made up of amphiphilic lipids, which delimit an internal aqueous compartment. This lipid bilayer is typically made up of lipids, which are biocompatible as well as

biodegradable, found in biological membranes. Sphingomyelin, glycerophospholipids, and phosphatidylcholine are common liposome components.

Cholesterol, a key component of the cellular membrane, is widely used in liposome formulations because it reduces bilayer permeability and improves liposome stability *in vivo*. Liposomes have been widely used to deliver drugs to the brain, treat cerebral ischemia, for opioid peptides delivery, and to treat brain cancers [8].

3.1.2. Solid Lipid Nanoparticles—Solid lipid nanoparticles (SLN) are a type of lipid-based nanocarrier having a solid hydrophobic lipid core that can disintegrate or distribute the drug. Biocompatible lipids, such as fatty acids, triglycerides, or waxes, are used to produce them. Their small size (around 40–200 nm) allows them to pass through the BBB's tight endothelial cells and escape the reticuloendothelial system (RES). SLN can enhance a drug's ability to cross the BBB, and it is a potential drug targeting system for treating CNS-related disorders [10].

3.2. Polymer-Based Nanoparticles

3.2.1. Polymeric Nanoparticles—Polymeric NPs consist of a core polymer matrix wherein drugs can be inserted, with sizes ranging from 60 to 200 nm [11]. A variety of materials have been used for drugs delivery, many of which disintegrate inside the body, including polyglycolide (PGA), poly(lactide-co-glycolides) (PLGA), polylactides (PLA), polycyanoacrylates, polycaprolactone, and polyanhydrides [12]. Natural polymers, like chitosan, can also be used despite the development of different synthetic and semi-synthetic polymers [13].

3.2.2. Polymeric Micelles—Amphiphilic copolymers deposit in aqueous solutions and form spheroidal structures called polymeric micelles, with a shell (hydrophilic) and a core (hydrophobic), as well as a high degree of stability [14]. Adhesion among core chains or between the shells can improve stability. The ability to make them responsive to external stimuli (light, pH, temperature, ultrasound, *etc.*) is another tunable characteristic [15], allowing for the controlled release of encapsulated drugs. The Pluronic type, a block copolymer derived from propylene oxide and ethylene oxide, is one of the most widely used polymers [15, 16].

3.2.3. Dendrimers—Dendrimers are tree-like structures with branched polymers. In water, a dendrimer is usually symmetric around the core and takes on a spheroidal three-dimensional form upon adequate expansion [17]. A central core with at least two identical chemical functions can be identified in its structure; repetitive units of other molecules can emerge from these groups, each with at least one branching junction. Chain and branching repetitions provide a sequence of radially concentric layers with increasing density. As a result, the structure is firmly packed near the edge and loosely packed in the centre, leaving gaps that are critical for the entrapment of drugs. PAMAM or poly(amidoamine) is likely the most well-known compound for dendrimer production [8].

3.3. Gold and Silver Nanoparticles

Gold nanoparticles (AuNPs) are an interesting system with unique properties that can be used in a variety of theragnostic applications. Biocompatibility, integration with diverse functional moieties, and ease of modification into various forms and sizes are all important features that drive researchers to focus on their applications for the diagnosis and treatment of cancer. Covalent bonds or electrostatic attraction are used to load therapeutic compounds onto AuNPs [18]. One of the essential qualities of AuNPs is their size variability, which allows them to travel through the circulatory system more easily. AuNPs can be directed to tumour cells/surfaces through free circulation [19].

3.4. Carbon Nanotubes

Carbon nanotubes (CNTs) are divided into two types based on their structure and diameter: single-walled CNTs (SWNTs) and multi-walled CNTs (MWNTs). The MWNTs are made up of overlapping graphene, while the SWNTs are made up of monolithic cylindrical graphene [20]. Carbon nanotubes are a choice best suited for large-scale biomedical applications owing to their physical and chemical properties, such as mechanical strength, surface area, electrical and thermal conductivity, and metal properties. Carbon nanotubes can also absorb light in the near-infrared (NIR) region, which results in the heating up of nanotubes as a result of the thermal effect, allowing them to attack tumor cells. Carbon nanotubes in their natural forms enhance noninvasive biofilms penetration and are considered extremely capable carriers for the delivery of different therapeutic compounds into living cells. Because of the adaptability of carbon nanotubes, drugs like paclitaxel are assembled with them and delivered for treating cancer both *in vitro* as well as *in vivo* [21].

3.5. Magnetic Nanoparticles (MNPs)

The majority of MNPs are made up of ferromagnetic iron oxide (Fe3O4). They are typically 1–100 nm in diameter and are undetectable to the human eye [22]. MNPs can be modified to treat cancer by adding a peptide or antibody, that is specific to cancer cells, to their surface [23]. They can assist in delivering targeted therapy to specific bodily areas for biological applications. MNPs can be injected directly into the bloodstream and redirected to a specific target using an external magnetic field [18]. Particles can be designed to carry a drug that is delivered after reaching the target site [23]. Nanoparticles used for brain drug delivery are shown in Fig. (1).

4. HOW NANOPARTICLES CAN CROSS THE BBB

The interplay between the BBB and nanoparticles on their intracellular traffic channels determines the efficiency of nanoparticles for various brain diseases and brain cancers. The way through which nanoparticles can reach the brain is shown in Table 1.

4.1. Crossing Without Functionalization

Even when there is no specific functionalization, some nanoparticles, such as gold and silica NPs, can cross the BBB and aggregate in neurons by an unknown mechanism [24, 25].

4.2. Adsorptive-Mediated Transcytosis

This theory is driven by the fact that cationic proteins can bind as well as cross the BBB. This method is dependent on appropriate NP surface functionalization, which facilitates electrostatic interaction with the BBB luminal surface. Because endothelial cells have a negative charge, imposing a positive charge on the surface of NPs can trigger this sort of interaction [26, 27].

The lower endocytic rate of brain endothelial cells (a key feature of the high BBB impermeability) is harnessed to boost preferential retention of protein-binding ligands on brain's endothelial cell surface over peripheral endothelial cells. Nanoparticles that can successfully attach to the selectively labeled endothelium are thereby directed exclusively to the brain microvasculature, with negligible deposition in peripheral organs. This method creates the requisite brain specificity for nanoparticles' administration, thus solving the targeting problems [28].

4.3. Receptor-Mediated Transcytosis

Drugs are delivered across the endothelium of the BBB utilizing functionalized NPs in this method. It relies on the existence of specific receptors on the cell's luminal surface to use a transcytosis physiological process [29].

4.4. Retrograde Transport

Some nanocarriers may be able to go from nerve terminals to the nerve cell body in the CNS by transsynaptic retrograde transport. Although polyethyleneimine- and other polyplexes-treated nanoparticles show active retrograde transport, when they reach the neuronal body, they are unable to exert efficient biological activities [30].

4.5. The BBB Breakdown

In neuroinflammatory diseases, the BBB breaks down. Tight junctions on the BBB can be opened spontaneously and temporarily by NPs, resulting in increased paracellular permeability. This method is widely and successfully used to deliver drugs to tumour sites [31].

4.6. Exploiting Monocyte/Macrophage Infiltration in the CNS

In different neurological disorders, infiltration of monocyte/macrophage in the CNS is involved in brain injury, neuroinflammation, and development of the lesion. Crossing the BBB by immune-activated macrophages indicates potential NP-based treatment methods in the future. This can be achieved in two ways: 1. By inserting NPs into monocytes (via phagocytosis), which can be utilized as Trojan horses to get through the BBB, or 2. by creating NPs that resemble monocytes. Boosting the phagocytosis of NPs by monocytes could be thought of as a novel strategy for drug delivery across the BBB, and NPs that imitate immune cells may be beneficial in treating brain-related illnesses and will probably be given more attention in the coming years [8].

4.7. Carrier Mediated Transcytosis

Many small compounds pass across the BBB by a carrier-mediated transcytosis, which is a substrate-specific mechanism. The large neutral amino-acid transporter type 1 (LAT1), which serves as a carrier for phenylalanine and 10 other major amino acids with a neutral charge and a few tiny neutral amino acids with lesser affinity, is an example of carrier-mediated transport. However, its mechanism is saturable owing to carrier necessity [7].

Tight junctions restrict the passive diffusion of hydrophilic solutes through paracellular diffusion, which is the transfer of molecules across the BBB through intercellular spaces between epithelial cells. Water-soluble compounds must thus penetrate the BBB actively through transcellular diffusion involving specialised carriers [32].

The different mechanisms through which nanoparticles cross the BBB are depicted schematically in Fig. (2).

4.8. Improving Efficiency of Nanoparticles

A question that arises while developing NPs for delivery across the BBB is if they follow a predictable pattern to deliver the drug successfully to the target site (brain). Despite the lack of a specific pattern, some of the features of NPs themselves, such as appropriate size and charge, could be helpful in successful drug delivery. Applying the following strategies could help in efficient drug delivery.

- Nanoparticles having a size less than 200 nm have a better probability of crossing the BBB effectively (*via* clathrin-mediated endocytosis) [33].
- The endothelial cell membrane has a negative charge, and hence, NPs with a positive charge can transverse the BBB (via adsorptive transcytosis) more easily than those with a negative or neutral charge [34].
- Adding numerous affinity ligands on NPs' surface can prevent endocytosis by endothelial cells, causing the drug-loaded NPs to stay connected to the endothelial cell membrane. This problem can be solved by using fewer ligands that have a higher affinity for the receptor [35].
- Using cell-penetrating peptides aids in circumventing the endocytotic route and transporting the drug-carrying NPs straight to the cytoplasm of the cell [36].
- Using ligands like PEG increases the circulation time of NPs, resulting in increased brain absorption [34].

Nanoparticles are often evaluated in a variety of rodent strains. However, it should be noted that when testing them on experimental animals, a variation in the BBB permeability is possible, as it has been observed in human disorders [37]. This would result in the BBB crossing efficiency that differs from that seen in wild-type animals. As a result, for the nano-particles crossing the BBB, assays should be performed in the most suitable animal models [38–43].

5. NANOTECHNOLOGY FOR THE DIAGNOSIS OF BRAIN CANCER AND ALZHEIMER'S DISEASE

The accuracy of clinical diagnosis can be improved by using innovative biosensor-based nanotechnology, which allows various abnormal tissues or organs to be diagnosed early and more precisely. A novel form of biosensor is the DNA biosensor. When nanoparticles are incorporated into DNA sensors, they become more sensitive and accurate. DNA sequences, mutations, and other information can be determined with the use of these DNA nanosensors. The chemiluminescence approach may detect a single misaligned base and a DNA molecule with the application of magnetic nanoparticles as a carrier of DNA or template for multiplication and amplification of DNA [44].

The identification and differentiation of distinct types of tumour cells with high specificity and efficiency, as well as assessment of tumour cell's drug resistance, are possible with the application of nano-biotechnology-based cell biosensors, which can greatly enhance cancer diagnosis and treatment. The nanotechnology-based microfluidic chip, a high-throughput analytical technique, has several advantages, including faster detection, lower cost, reduced energy consumption, and higher detection efficiency [45].

Early identification is critical for the efficient treatment of AD since neuronal damage and degenerative alterations begin before the appearance of clinical manifestations. To locate and identify amyloid plaques, most investigations use magnetic resonance imaging (MRI) using contrast-doped NPs or tagging NPs with fluorescent probes. Magnetic iron oxide NPs have an enormous surface area, strong magnetic characteristics, low cytotoxicity, outstanding biocompatibility and rapid degradation, and hence have received a lot of importance. Recently, localised surface plasmon resonance (LSPR), a technique for detecting molecular biomarkers, was tested for AD biomarkers [46]. Target bio-labelling of the affected regions of the brain was investigated as a potential technique for *in vivo* fast fluorescence imaging of AD. The treatment of brain areas with aqueous chloroauric acid (HAuCl4) solutions leads to the formation of Au (gold) salts, which in turn combine to form gold nanoclusters (Au NCs) that can be employed for fluorescence bio-imaging [47–63], Table 2.

6. NANOTECHNOLOGY FOR BRAIN TUMOR THERAPY

Nanomaterials have a unique advantage of being used as drug carriers owing to their large specific surface area and surface and interface effect. Some surface-modified NPs can avoid being detected by macrophages, allowing them to better target tumour tissues [64].

6.1. Passive Targeting

Therapeutics can be delivered effectively to intracranial tumors *via* intravenous administration of nanoparticles, which can permeate the BBB and concentrate selectively at tumor locations in comparison to drugs administered in solutions. These nanoparticles can be designed for brain-specific delivery, allowing hydrophobic and metabolically inert drugs to be delivered. Drug delivery to brain tumours by intravenously delivered nanoparticles may take advantage of the improved permeation and retention, in which the nanoparticles extravasate the leaky tumour vasculature, allowing them access to the tumour cells [4]. But

even so, increased permeation and retention can only be noted when the BBB is disrupted at the tumour site; however, because the disruption of the BBB is a characteristic of high-grade glioma, most tumours are linked to an intact BBB, making direct nanoparticle deposition within the brain tumour. In a C6 glioma rat model, an intravenous injection of doxorubicin, a P-gp substrate, as poly (butyl cyanoacrylate) nanoparticles, led to improved levels of doxorubicin in the target tissue, thereby indicating an improvement in tumoricidal action in comparison to the drug in solution. Furthermore, the nanoparticle-containing formulation is less cardiotoxic. On intravenous administration, cyanoacrylates have also shown tumour tissue accumulation. For brain tumor treatment, nanomedicines can also carry several drugs at a time. Chitosan surface-modified PLGA nanoparticles infused with carmustine and O6-benzyl guanine reduce MGMT, improving carmustine therapeutic efficacy. As compared to the two drugs injected separately in solution or carmustine alone infused as a nanoparticle, the above formulation was administered intravenously and led to superior survival rat models of glioma [4, 65].

6.2. Active Targeting

Carriers with various types of surface ligands are utilized in active targeting to traverse the BBB, or cell uptake takes place following extravasation across the leaky BBB [66]. TfR and Glut are two BBB transporters that have been explored for transferring intact drugs across the BBB [7]. Tf-c [RGDfK] paclitaxel micelles were produced and administered intravenously in the U87MG mouse model. Tf was incorporated to enable the BBB transport, in which c[RGDfK] facilitated micelle uptake by tumor cells. In comparison to Taxol (commercial formulation), the formulation of these micelles promoted drug deposition in the brain and exhibited a superior anti-cancer activity [67]. Using 2-deoxy-D-glucose-modified poly(ethylene glycol)-co-poly(trimethlene carbonate) nanoparticles of paclitaxel, GLUT was used to traverse the BBB. As a comparison to Taxol and plain nanoparticles, the 2-deoxy-D-glucose moiety permits the drug to accumulate in the brain, resulting in better survival in an RG2 animal glioma model [68].

7. NANOPARTICLES FOR ALZHEIMER’S DISEASE THERAPY

Eliminating the limitation of the BBB, as with brain tumors, could modernize several CNS therapies, like Alzheimer’s disease. Currently, there is limited treatment available for AD and reversing the further progress is challenging. The deposition of amyloid plaques, which leads to the death of neurons, is a hallmark of this disease [69].

Currently, existing treatments for Alzheimer’s disease only treat the symptoms, but recent research has focused on drugs called “neuroprotective drugs,” which could slow or even stop the disease from progressing further by targeting the pathological process [70]. A more speculative strategy to treating Alzheimer’s disease is to combine neuroprotective drugs with “regenerative agents,” which can assist in tissue repair. “Disease-modifying approaches” refer to a combination of neuroprotective and regenerative agents. Nanotechnology-based therapeutic strategy for treating Alzheimer’s disease involves both neuroprotection and regeneration; thus, several nanocarriers were investigated recently to improve the

bioavailability and efficiency of several AD therapeutic drugs [71, 72]. Various types of nanoparticles used for AD therapy are shown in Fig. (3).

7.1. Neuroprotective Potential of Nanotechnology

Aβ oligomers and free radicals are the major causes of neurotoxicity in the pathophysiology of AD. Some nanotechnology-based techniques can prevent neurons from Aβ toxicity by suppressing amyloid oligomerization and/or aggregation of Aβ oligomeric species. Other neuroprotective nanotechnology methods are those that prevent neurons from free radical oxidative stress [71].

Antioxidants-loaded NPs have the ability to neutralise free radicals produced during AD. Fullerene and its derivatives are the most common nanomaterials employed in neuroprotection. Free radicals and calcium concentration in nerve cells are restricted by fullerenol-mediated neuroprotective effects. There are ongoing advancements in the applicability of nanotechnology in neuroprotection. The use of carbon nanotube (CNT) is one of the examples. Nanotube electrodes reverse the neuronal damage by forming nanoscaffolds [73].

7.1.1. Nanogels—Nanogels limit the amyloidogenesis process by controlling protein folding and aggregation (Aβ anti-assembly technique) [74]. Nanogels are cholesterol-bearing pullulan (CHP)-based hydrogel nanoparticles. Maltotriose (a trisaccharide comprised of three glucose molecules connected by 1,4 glycosidic linkages) units constitute pullulan, a natural water-soluble polysaccharide polymer. Because this approach avoids Aβ oligomerization, the concentration of deadly Aβ oligomeric species is reduced [71]. In some cell cultures, especially cortical and microglial, the use of CHP nanogels resulted in a considerable reduction in Aβ42 toxicity [75].

7.1.2. Fullerene—Neuroprotective molecules can be formed based on fullerene (C60). Because of the molecular structure that enables it to be connected (and functionalized) in a 3-dimensional orientation, fullerene has antioxidant and free radical scavenging properties. In cultured cortical neurons, the action of carboxy fullerenes (a malonic acid derivative of C60, {C63[(COOH)2]3}) on Aβ42 mediated oxidative stress and neurotoxicity was observed, and it was found that it prevented apoptosis by Aβ42 [76]. Fullerenols are water-soluble derivatives of fullerene and have exhibited neuroprotective benefits against Aβ42, owing to their antioxidant properties [77]. Potential applications of functionalized fullerene and its derivatives (caboxyfullerene, hydroxyfullerene (fullerenols), and C60HyFn) are being investigated for the development of effective treatment for AD.

7.1.3. Nano-Ceria—Nanoceria is a cerium oxide (CeO2) nanoparticle that has been shown to have a neuroprotective benefit in *in vitro* AD model [78]. These neuroprotective properties are mostly owing to their antioxidant properties [79]. Nanoceria also shields neurons from Aβ cytotoxic activity by altering an intracellular signaling pathway implicated in both cell death as well as neuroprotection [78].

7.1.4. Dendrimers—Dendrimers provide a multifunctional anti-myeloid approach. Dendrimers use an Aβ anti-assembly strategy by attaching to peptide monomers or

inhibiting the ends of protofibrils and fibrils. Dendrimers are also involved in minimizing Aβ cytotoxic effects [69]. However, due to the potential toxicity of dendrimers on cells, this approach requires more research before being used *in vivo*.

7.1.5. Gold Nanoparticles—The resolubilization of fibrillar amyloid species is one of the proposed anti-myeloid strategies. Gold nanoparticles (AuNPs) can disintegrate amyloid plaques in weak microwave fields. AuNPs were created to disintegrate and minimize Aβ plaques by supplying local heat energy at the molecular level. When a weak microwave field is supplied, AuNPs connect to a target, such as Aβ, and release thermal energy, which dissolves fibril binding [80].

7.1.6. Diamondoid Derivatives—In nanotechnology, diamondoids are among the most potential molecular entities [81]. Memantine, a diamondoid-based drug, inhibits the advancement of AD [82]. Memantine is a medication that has been licensed by the FDA for AD treatment.

Memantine suppresses the excessive activity of NMDA receptors while leaving normal activity unaffected [83]. Despite memantine having already been approved by the FDA, research is currently being conducted on other derivatives that may have better neuroprotection and probably regeneration abilities, as well as applications for treating diseases involving glutamatergic dysfunction.

7.2. Nanocarriers

Nanomedicine involves a lot of applications, one of which is targeted drug delivery. The BBB acts as an extra barrier to the flow of a range of chemicals into the CNS tissue, making disorders of CNS significantly more severe [84]. The application of biocompatible nanoparticles to help medicinal drugs cross the BBB has gained a lot of attention in the last decade [85]. The following sections address nanocarrier systems that have been proposed for delivering therapeutic agents for Alzheimer's disease into the brain. Different types of nanocarriers used for the delivery of Alzheimer's disease have been described in Table 3 [86–102].

CONCLUSION

There is a need for further research on the diagnosis and treatment of BC and AD; several nanoparticle formulations have proven to be potential approaches in animal models of these diseases, and a few of them have even progressed to clinical testing. Many studies have introduced nanotechnology in the diagnostics of BC and AD by administering drug-loaded nanoparticles, thus allowing target cells/tissues to be imaged with this new theranostics. Drugs administered through nanotechnology can combat the BBB and can reach the target with good potential. There is a need for more research regarding the safety assessment of drug-loaded nanoparticles in diagnostics and therapy of BC and AD in a complex biological milieu.

ACKNOWLEDGEMENTS

The authors are thankful to the Dean, college of Pharmacy, and the rector of University of Hail for their constant encouragement.

LIST OF ABBREVIATIONS

BC	Brain Cancer
BBB	Blood-Brain Barrier
VEGF	Vascular Endothelial Growth Factor
PLGA	Poly(lactides-co-glycolides)
AD	Alzheimer's Disease
Aβ	Amyloid-β
CNS	Central Nervous System
NPs	Nanoparticles
SSRIs	Selective Serotonin Reuptake Inhibitors
BTB	Brain Tumor Cell Barrier
SLN	Solid Lipid Nanoparticles
RES	Reticuloendothelial System
PLA	Polyactides
PGA	Polyglycolides
PAMAM	Poly(amidoamine)
AuNPs	Gold Nanoparticles
CNT	Carbon Nanotubes
SWNTs	Single-walled Carbon Nanotubes
MWNTs	Multi-walled Carbon Nanotubes
NIR	Near-infrared
MNPs	Magnetic Nanoparticles
Fe3O4	Ferromagnetic Iron Oxide
PEI	Polyethylenimine
DNA	Deoxyribonucleic Acid
SERRS	Surface-enhanced Resonance Raman Scattering

MRI	Magnetic Resonance Imaging
PA imaging	Photoacoustic Imaging
FL Imaging	Fluorescence Imaging
FUS	Focused Ultrasound
MSOT	Multispectral Optoacoustic Tomography
PEG	Polyethylene Glycol
PET	Positron Emission Tomography
CT	Computed Tomography
MGMT	O [6]-methylguanine-DNA methyltransferase
TfR	Transferrin Receptor
Tf-c	Thin-film Composite
GLUT	Glucose Transporter
CHP	Cholesterol Bearing Pullulan
CeO2	Cerium Oxide
FDA	Food and Drug Administration
NMDA	N-methyl-D-aspartate
PnBCA	Poly n-butyl Cyanoacrylate
ORMOSIL	Organically Modified Silica

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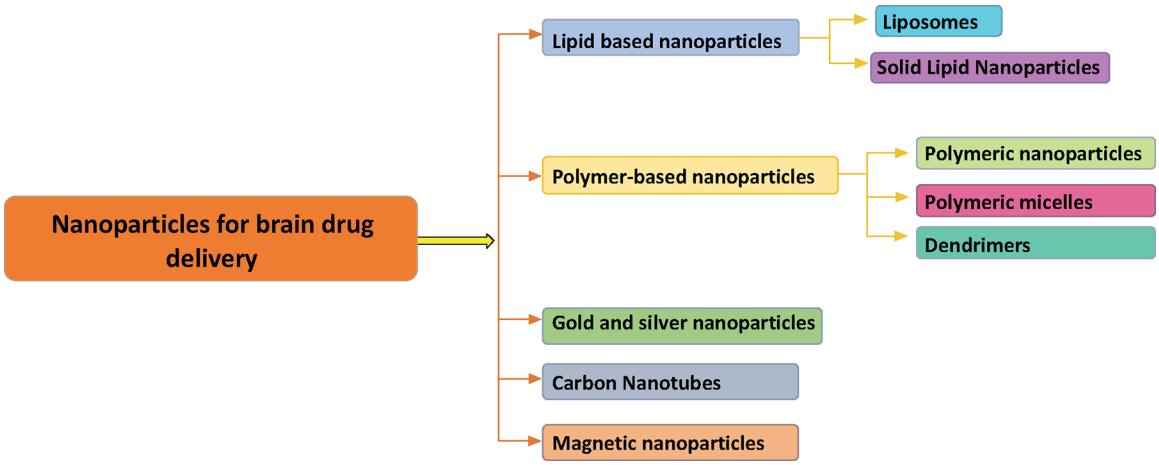

Fig. (1).

Types of nanoparticles for brain drug delivery. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

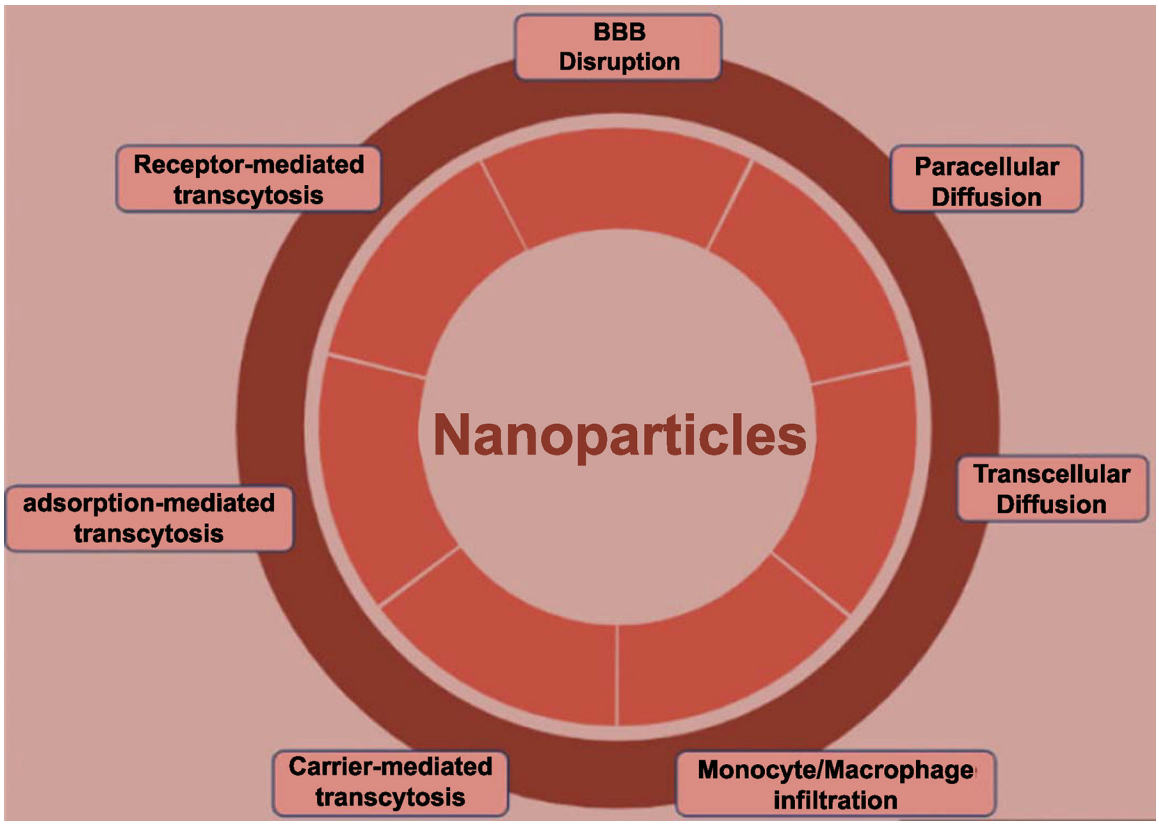

Fig. (2).

Mechanisms through which nanoparticles cross the BBB. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

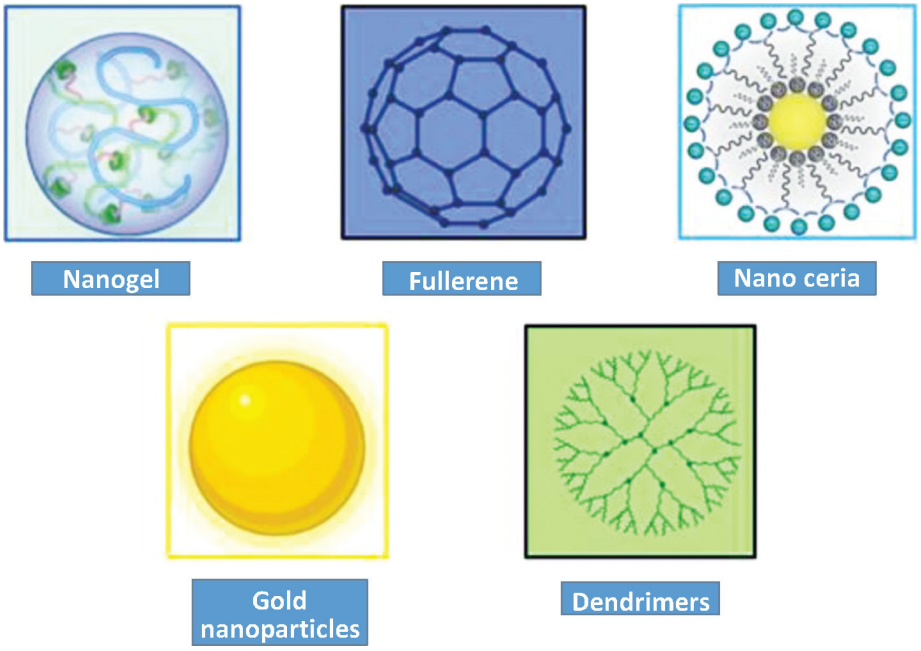

Fig. (3).

Nanoparticles used for the treatment of AD. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1.

Different ways through which NPs can reach the brain.

S. No.	Mechanism	Type of Nanoparticle	Disease	References
1.	Crossing the BBB without functionalization	Gold and silica NPs	Stroke, Brain tumours	[38]
2.	Adsorptive mediated transcytosis	SLN	Brain tumour	[39]
3.	Receptor-mediated transcytosis	NPs made of gold, PLGA, chitosan, dendrimers, and liposomes (Caspase inhibitors, endomorphin, tamoxifen, and tramadol)	Neurological diseases	[40]
4.	Retrograde transport	NPs modified with PEI and other polyplexes	Neurological diseases	[41]
5.	The BBB breakdown	NPs smaller than 20 nm	Brain tumours	[42]
6.	Exploiting monocyte/macrophage infiltration in CNS	Nanoparticles are embedded in activated monocytes (Trojan horses) or NPs that mimic activated monocytes	Brain tumours, Alzheimer's disease	[43]

Table 2.

Nanotechnology in the diagnosis and imaging of brain cancer/tumours and Alzheimer's disease.

S. No	Imaging Technique	Nanotechnology Used	References
1.	Surface-enhanced resonance Raman scattering imaging (SERRS)	SERRS NPs with 68Ga comprised of gold core and silica shell	[48, 49]
2.	Magnetic resonance imaging (MRI)	Iron oxide NPs' surface decorated with peptides; gadolinium oxide-based NPs	[50, 51]
3.	Photoacoustic (PA) imaging	Silicon quantum sheets, molybdenum di-sulfide nanosheets conjugated with indocyanine green	[52, 53]
4.	Fluorescense (FL) imaging	Gold NPs	[54, 55]
5.	Focused ultrasound (FUS)	Cisplatin gold NP conjugates, mesoporous organo-silica NPs	[56, 57]
6.	Multimodal imaging	SERRS-MSOT*-nanostar with gold core embedded in silica coat functionalized with PEG, SERRS-MRI gold	[58, 59]
7.	Positron emission tomography (PET)	Alanine modified gadofullerene NPs, self-assembled amphiphilic dendrimer nano-system	[60, 61]
8.	Computed tomography (CT)	Transferrin conjugated liposome, Lanthanide NPs	[62, 63]

Table 3.

Different Alzheimer's drugs delivered through nanocarriers.

Type of Nanocarrier	Drug Used	Pharmacological Activity	Nanotechnology Used	References
Curcuminoids nanocarrier	Curcumin	Anti-amyloid assembly, anti-oxidant and anti-inflammatory	Poly n-butylcyanoacrylate (PnBCA) nanocapsules	[86, 87]
Cholinesterase inhibitors nanocarriers	Rivastigmine and Tacrine	Inhibits the enzyme that degrades acetylcholinesterase	Polysorbate 80 coated polymeric Poly n butyl cyanoacrylate (PnBCA) nanocapsules	[88, 89]
Acetylcholine nanocarriers	Acetylcholine	Delivery of acetylcholine	Single w II carbon nanotubes (SWCN)	[88, 90]
Hormone nanocarriers	Estrogens and androgens	Inhibits Aβ accumulation, cytotoxicity, and neurotoxicity	Chitosan and poly(lactide co glycolide acid) (PLGA) nanoparticles	[88, 91–95]
Green tea polyphenol nanocarrier	Green tea polyphenol, epigallocatechin 3 gallate	Antioxidant activity reduces Aβ production	Lipid nanocarrier	[5, 67, 96]
Chelator nanocarriers	Iron chelators Copper chelators	Aβ aggregation (and then precipitation)	Chelator nanoparticle system (CNPS)	[97, 98]
Anti-oxidant nanocarrier agent	Ferulic acid	Reduced ROS production, normalized mitochondrial membrane potential, and decreased cytochrome C release	Solid lipid nanoparticles (SLN)	[99, 100]
Gene nanocarriers	Genetic materials	Minimizing the enzymatic degradation of genetic materials	Polymeric, ceramic, and amino-terminated organically modified silica (OR-MOSIL) nanoparticles	[101, 102]