Neurochemistry International 145 (2021) 105008

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Biomaterials in treatment of Alzheimer's disease

Mukta Agrawal [a], Eluri Prathyusha [g], Hafiz Ahmed [g], Sunil Kumar Dubey [c,e], Prashant Kesharwani [d], Gautam Singhvi [e], V.G.M. Naidu [f], Amit Alexander [b,*]

[a] Rungta College of Pharmaceutical Sciences and Research, Kohka-Kurud Road, Bhilai, Chhattisgarh, 490024, India
[b] Department of Pharmaceutical Technology (Formulations), National Institute of Pharmaceutical Education and Research (NIPER-Guwahati), Sila Katamur (Halugurisuk), Changsari, Kamrup, 781101, Guwahati, Assam, India
[c] Emami Ltd., Anandapur, Kolkata, 700107, India
[d] Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, 110062, India
[e] Department of Pharmacy, Birla Institute of Technology and Science, Pilani, Pilani Campus, Rajasthan, 333031, India
[f] Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER-Guwahati), Sila Katamur (Halugurisuk), Changsari, Kamrup, 781101, Guwahati, Assam, India
[g] Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER-Guwahati), Sila Katamur (Halugurisuk), Changsari, Kamrup, 781101, Guwahati, Assam, India

ARTICLE INFO

Keywords:
Biomaterials
Alzheimer's disease
Functional biomaterials
Nanocarriers
Liposome
Dendrimer

ABSTRACT

Alzheimer's disease (AD) is a non-recoverable progressive neurodegenerative disorder most prevalent but not limited to the old age population. After all the scientific efforts, there are still many unmet criteria and loopholes in available treatment and diagnostic strategies, limiting their efficacy. The poor drug efficacy is attributed to various biological hurdles, including blood-brain barrier (BBB) and peripheral side effects as most prominent ones and the lack of promising carriers to precisely deliver the drug to the brain by conserving its therapeutic potency. The increasing disease prevalence and unavailability of effective therapy calls for developing a more innovative, convenient and affordable way to treat AD. To fulfill such need, researchers explored various biomaterials to develop potential vectors or other forms to target the bioactives in the brain by preserving their inherent properties, improving the existing lacuna like poor solubility, permeability and bioavailability etc. and minimize the side effect. The unique characteristic properties of biomaterials are used to develop different drug carriers, surface modifying target active ligands, functional carriers, drug conjugate, biosensing probe, diagnostic tool and many more. The nanoparticulate system and other colloidal carriers like hydrogel and biodegradable scaffold can effectively target the drug moieties to the brain. Also, the use of different target-acting ligands and stimuli-responsive carriers assures the site-specificity and controlled release at the desired site by interaction with receptors and various exo- and endogenous stimuli. This review article has highlighted the application of biomaterials for targeting the drug to the brain and as promising diagnostic tools to detect the markers for better AD management. The work particularly focuses on the use of biomaterials as smart drug carriers including pH, thermo, photo, electro and magnetically triggered system; novel drug carriers for brain targeting including polymeric carriers (polymeric nanoparticle, dendrimer and polymeric micelle); lipid carrier (liposome, nanoemulsion, NLC and SLN); inorganic nanoparticles (quantum dots, gold nanoparticles etc.); and other drug vectors (hydrogel, biodegradable scaffold, and carbon nanotube) in treatment of AD. It also highlighted the application of some novel carrier systems and biomaterials as biosensor and other diagnostic tools for early and precise AD diagnosis.

* Corresponding author. Department of Pharmaceutical Technology (Formulations), National Institute of Pharmaceutical Education and Research (NIPER-Guwahati), Department of Pharmaceuticals, Ministry of Chemicals & Fertilizers, Govt. of India, Sila Katamur (Halugurisuk), Changsari, Kamrup, 781101, Guwahati, Assam, India.
E-mail addresses: amit.alexander@niperguwahati.ac.in, itsmeamitalex@gmail.com (A. Alexander).

https://doi.org/10.1016/j.neuint.2021.105008
Received 4 November 2020; Received in revised form 1 March 2021; Accepted 1 March 2021
Available online 5 March 2021

1. Introduction

Alzheimer's disease, usually recognized as dementia, is a progressive, irretrievable, multifactorial neurodegenerative disorder characterized by the gradual decay of nerve cells and synapses all over the brain. Such continuous and irreversible damage of nerve cells leads to profound deterioration of the brain's cognitive, memory, and behavioral functions (Hampel et al., 2020). However, dementia and AD[1] are two distinct terms closely related to each other concerning the physiological symptoms. As per WHO, dementia is described as a syndrome or a group of symptoms including impaired cognitive functions and deficit of memory, learning and behavioral abilities. In contrast, AD is a disease which gets worsens with time and age. It is considered as most common type or cause of dementia, contributing around 60–70% of dementia cases worldwide. AD is a group of behavioral syndromes, including memory impairment, cognitive loss, learning and thinking disabilities, mood swings, difficulty in routine activities and many more. After such extensive research still, the exact pathological cause of AD is unknown. However, various hypotheses have been suggested to define possible causative factors of AD, including amyloid cascade hypothesis, tau hyperphosphorylation, mitochondrial dysfunctioning, oxidative stress, genetic mutation, and some others like exposure to any toxin, environmental stimulus and any physical injury.

Frequent growing incidences of AD urges for a potential diagnostic and therapeutic tool. Presently, only five molecules, namely galantamine, donepezil, tacrine, rivastigmine and memantine, have been approved by USFDA[2] for AD therapy, and that too only has disease-modifying or symptomatic effect. No potential cure is available to act on the root cause of disease and, the approved medicines exert severe side effects upon long-term use, which can't be avoided. Another critical concern is high-cost therapy, which is almost unaffordable for most of the AD population as they belong to a lower-middle economic class of society. Hence, this cost indirectly burdens government funds. Thus, the WHO[3] declared it a world socio-economic burden with a $600 billion yearly cost (Kaushik et al., 2016). Looking at all the facts, the need of the time is to develop promising drug delivery vectors that precisely deliver the drug to the target site of the brain with minimum systemic exposure to alleviate the associated adverse effects at an affordable cost.

The brain is a highly delicate organ, protected by various physiological measures, including the BBB,[4] meninges, BCSFB[5] and efflux transport. Among all these, the BBB appears as the foremost constraint for the bioactives to reach the brain. It is a protective layer that shields the brain tissues from exposure to the general circulation. It imitates an essential protective mechanism that obstructs the entry of harmful and undesirable chemicals, stimuli, and any deleterious substance to the brain and maintains homeostasis (Agrawal et al., 2020b). The BBB is primarily composed of BCECs[6] joined together by the tight junction and supported by astrocytes, pericytes and nerve cells. Tight junction seals the adjoining BCECs, imparts high TEER[7] between blood and brain and thus restricts paracellular transport of any foreign moiety through passive diffusion to the brain. Such an arrangement makes BBB a highly selective semipermeable barrier that permits small, low molecular weight lipophilic moieties. However, BBB is adorned with special transporters like receptors, transporter proteins, ion channels etc., to enable the transport of essential nutrients to the brain. The transport mechanism of BBB includes passive diffusion, receptor-mediated transcytosis, absorption mediated transcytosis, carrier-mediated transport, efflux transport and ion channel transport. These passages could be used to deliver the drug across BBB effectively. Researchers have explored numerous natural and synthetic biomaterials to design promising vector or drug carrier systems to target the brain and find a potential treatment of AD to fulfill the objective. In this review, we have discussed some common biomaterials and their application in developing novel drug carriers, including the role of functional biomaterials in brain targeting. Precisely, we have highlighted the application of thermoresponsive, pH triggered, photosensitive, electroresponsive and magnetically triggered biomaterials along with their role in developing different novel drug carriers like polymeric nanoparticle, dendrimer, micelle, liposome, nanoemulsion, SLN,[8] NLC,[9] gold nanoparticle, quantum dots, magnetic nanoparticle, hydrogel, biodegradable scaffold and Carbon nanotube.

2. Pathophysiology of AD

As discussed earlier, AD is a multifactorial neurodegenerative disorder caused by various pathophysiological abnormalities. It has been more than a century since the discovery of AD, and we still do not know its exact etiology. Some physiological changes or abnormalities like extracellular Aβ plaque, tau hyperphosphorylation, cholinergic imbalance, excitotoxicity, mitochondrial dysfunctioning etc., and risk factors including aging, genetic mutation, environmental factors etc., are proposed and well accepted as AD etiology. However, the triggering factors of such abnormalities and mutation are not completely known. Based on investigations, various hypotheses are proposed to ease the AD-related investigations and find the appropriate therapies discussed below.

2.1. Cholinergic hypothesis

It is the first proposed and most accepted hypothesis of AD, nearly seen in most AD cases. This hypothesis stated that neuron degeneration in AD results from impaired synthesis of ACh[10] in the brain. Destruction of cholinergic neurons hampered the ACh synthesis and also diminish acetylcholine uptake by neurons. The reduced ACh synthesis by the cholinergic neurons significantly affects the neurotransmission, damages the synapse and results in loss of cognitive, learning and memory function of the brain (Dubey et al., 2019). Cholinergic dysfunctioning is a well-accepted characteristic of AD, although cholinesterase inhibitors like donepezil, galantamine, rivastigmine etc., only mitigate the symptoms of AD and not the disease progression. Such clinical observations indicate that cholinergic imbalance could be just clinical feature of AD and for effective treatment, a better understanding of AD etiology is highly desirable.

2.2. Amyloid cascade hypothesis

Amyloid cascade hypothesis is the most prevailing theory, proposed around 30 years ago in 1991 to explain the etiology of AD neurodegeneration (Liu et al., 2019). This hypothesis suggests that Aβ plaque formation or Aβ accumulation in the brain interrupts neuron functioning and causes nerve cell death leading to neurodegeneration. A pathogenic mutation in the APP[11] gene on chromosome 21 results in APP aberrant metabolism, leading to th3e formation of toxic or abnormal Aβ deposits and aggregates. APP is an integral membrane protein composed of 695 AA[12] residues, usually expressed in different cells and neuronal synapses. Hydrolytic cleavage of APP gives rise to various Aβ peptides consisting of 39–43 residual AA (Du et al., 2018). The hydrolytic cleavage of APP takes place in two ways (i) α-pathway and (ii) β-pathway. In the first

[1] Alzheimer's disease.
[2] United State Food and Drug Administration.
[3] World Health Organization.
[4] Blood brain barrier.
[5] Blood cerebrospinal fluid barrier.
[6] Brain capillary endothelial cells.
[7] Transendothelial electrical resistance.
[8] Solid lipid nanoparticle.
[9] Nanolipid carrier.
[10] Acetylcholine.
[11] Amyloid precursor protein.
[12] Amino acid.

path, APP is initially hydrolyzed through α-secretase enzyme followed by γ-secretase activity and produces non-toxic Aβ fibrils. Conversely, in the second pathway, APP cleavage is mediated by BACE1,[13] followed by γ-secretase and produces insoluble, toxic Aβ. The Aβ peptide produced by BACE1 further forms extracellular deposits or aggregates, leading to Aβ plaque or senile plaque formation and causing neurodegeneration (Fig. 1) (Dubey et al., 2019, 2020). In a healthy brain, APP cleavage usually occurs though α and γ-secretase and Aβ fibrils formed and thereby are disposed from the brain via the immune system. Some physiological abnormalities due to aging, genetic mutation or some other factors shift the APP hydrolysis to β-pathway, which cause damage of nerve cells and result in AD.

2.3. Tau hyperphosphorylation

Tau protein is a highly soluble, microtubule-associated protein mainly expressed in the neurons of the central nervous system, including glial cells and astrocytes and peripheral nerve cells. The primary function of the tau protein is to stabilize the microtubule assembly and facilitate nerve cell stabilization. Microtubules are essential components of the neuronal cytoskeleton and act as a conveyer belt for intracellular transport of various granules, vesicles, chromosomes, cell organelles such as mitochondria etc. These are small tubular structures composed of 13 filaments made up of a chain of two structural proteins called α and β-tubulin. The tubulin proteins are linearly arranged to form a sheet which rolls up and form tubules (Venkatramani and Panda, 2019). tau protein stabilizes this tubular structure of the microtubule and also provides flexibility as required. The structure of tau protein has four regions (i) acidic region or N-terminal, (ii) protein-rich region, (iii) microtubule-binding region and (iv) C-terminal. Microtubule binding region is responsible for interaction with tubulin protein and holds them together. It maintains the structure and stability of microtubules by two ways, either through isoforms or phosphorylation. An abnormal, excessive or hyperphosphorylation of tau transforms regular tau protein into PHF[14] and NFT[15] (John and Reddy, 2021; Laurent et al., 2018). Hyperphosphorylation of tau happens due to various physiological and metabolic abnormalities like peculiar Aβ, tau kinase, brain glucose metabolism and genetic mutation. It results in disassembly of microtubule and formation of insoluble toxic aggregates, PHF and NFT, which finally cause neuronal damage or death by destabilizing nerve structure, interfering with axonal transport and blocking the neuronal synapse (Fig. 2) (Gong and Iqbal, 2008). Thus, tau hyperphosphorylation became a major etiological factor of various neurodegenerative disorders, including AD.

2.4. Vascular hypothesis

The homeostasis of the brain microenvironment and metabolic function significantly depends upon the passage of micronutrients to the brain and clearance of waste materials through blood vasculature. Nerve cells, astrocytes, vascular cells and blood vessels are essential components of this neurovascular system that assist to maintain the integrity and regular functions of a healthy brain. A disturbance in this vascular transit interrupts the healthy routine of the brain and leads to various diseases, including different cerebrovascular and neurodegenerative disorders like AD. It was proven that AD causes the damage of brain microvasculature. Inversely, various *in vivo* studies report neurovascular damage or dysfunction prior to Aβ accumulation or onset of AD (Niwa et al., 2000; Ruitenberg et al., 2005; Smith et al., 1999). Unusual angiogenesis and age-induced deterioration of the cerebrovascular system affect the elimination of Aβ peptide through BBB, leading to regression of vessels and, consequently, brain hypoxia, hypoperfusion, and neurovascular inflammation. In addition, damage of BBB due to neuroinflammation and chemical imbalance of neural microenvironment results in loss of memory and cognitive function due to neuronal dysfunction.

2.5. Mitochondrial cascade hypothesis

The mitochondrial cascade hypothesis was first introduced by Swerdlow and Khan in 2004. This hypothesis stated the mitochondrial deregulation greatly affects the APP expression in nerve cells and its metabolism along with Aβ accumulation in SAD.[16] This theory has three main postulates; (i) mitochondrial function of an individual is predefined by genetic inheritance, (ii) age-related change in mitochondrial function is affected with various inherent and environmental factors and mitochondrial sinking leads to aging phenotype, and (iii) rate of mitochondrial deterioration or functional modulation significantly affect AD chronology. Damaged mitochondria are primarily responsible for ROS[17] production, which is a major factor of AD progression. Metabolite produced by mitochondrial TCA[18] cycle compounds/intermediates like fumarate, pyruvate, malate etc., are essential for neuronal longevity and epigenetic regulation (Matilainen et al., 2017). However, mitochondrial dysfunctioning significantly affect the metabolic functions of nerve cells and cause abnormal redox reaction, thus resulting in excessive free radical or ROS production. All these aberrant functioning of mitochondria finally leads to neurodegeneration and initiate and affect AD progression (Liu et al., 2019).

2.6. Oxidative stress

Oxidative stress is another important driving factor of neurodegeneration that worsens the disease progression. It is referred to as an imbalance between cellular antioxidants and pro-oxidants with disruption of mitochondrial redox circuitry. It is driven due to the excessive production of ROS inside the cells. In normal cells, ROS is usually produced during various metabolic reactions in different cell organelles, including ER,[19] mitochondria, peroxisome etc., and scavenged by antioxidants (Di Meo et al., 2016). Various external or internal factors like aging, disease condition, injury, shock, and other environmental factors interrupt cellular homeostasis and trigger uncontrolled ROS production. In the AD brain, nerve cells demonstrate decreased number of healthy mitochondria, and excessive oxidative damage alongside an insufficient amount of cellular antioxidants results in severe oxidative stress and neuronal damage. Increased oxidative stress and ROS level also worsen other pathological factors of AD, including Aβ aggregation, tau hyperphosphorylation and cause neural apoptosis. ROS shifts the APP hydrolysis to the β-secretase pathway and increases Aβ plaque formation (Dubey et al., 2019).

2.7. Neuroinflammation

Inflammatory responses of astrocytes and microglia in CNS[20] also significantly affect AD progression. Microglia are inherently macrophages of the brain or CNS region, contributing around 10–15% of brain cells. Studies demonstrated significantly higher activity of microglia in the AD brain as compared to the normal brain. Similarly, the accumulation of microglia near NFT, amyloid plaque and damaged neurons is also 2–5 folds higher than healthy cells. The overexpression of microglia, hyperactivation of histocompatibility complex and release of

[13] β-secretase enzyme.
[14] Paired helical-filament.
[15] Neurofibrillary tangle.
[16] Sporadic AD.
[17] Reactive oxygen species.
[18] Tricarboxylic acid.
[19] Endoplasmic reticulum.
[20] Central nervous system.

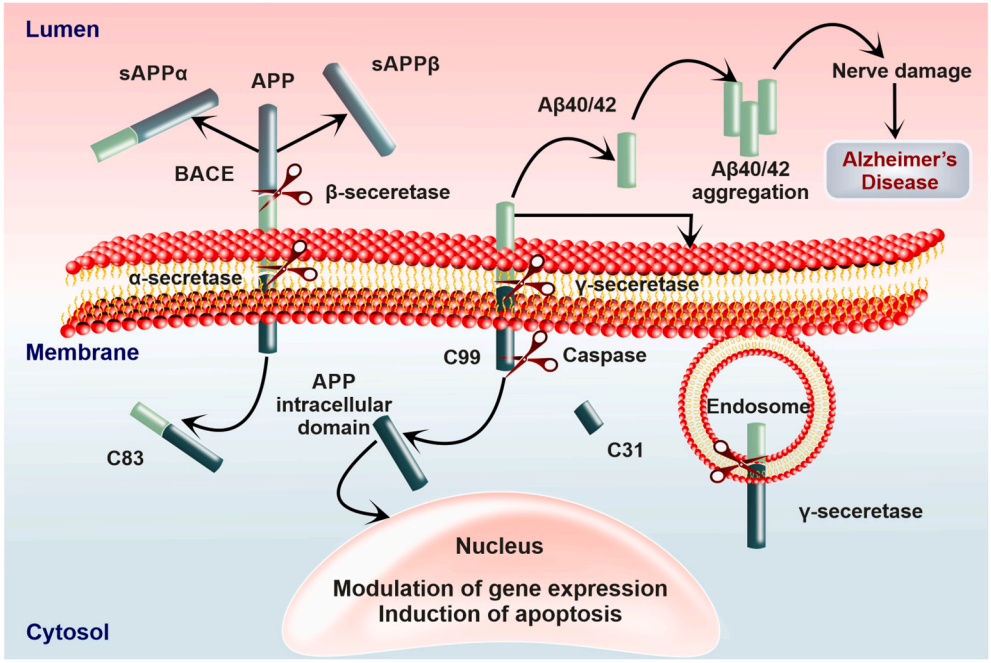

Fig. 1. APP cleavage through α-secretase forms non-toxic sAPPα and C83 residue, metabolized through a regular metabolic process. While hydrolysis through BACE or β-secretase forms soluble APPβ and leave C99 residue, which further cleaved through γ-secretase and results in insoluble Aβ40/42 fibrils. These Aβ40/42 fibrils get aggregated and lead to Aβ plaque formation that causes neuronal damage and AD.

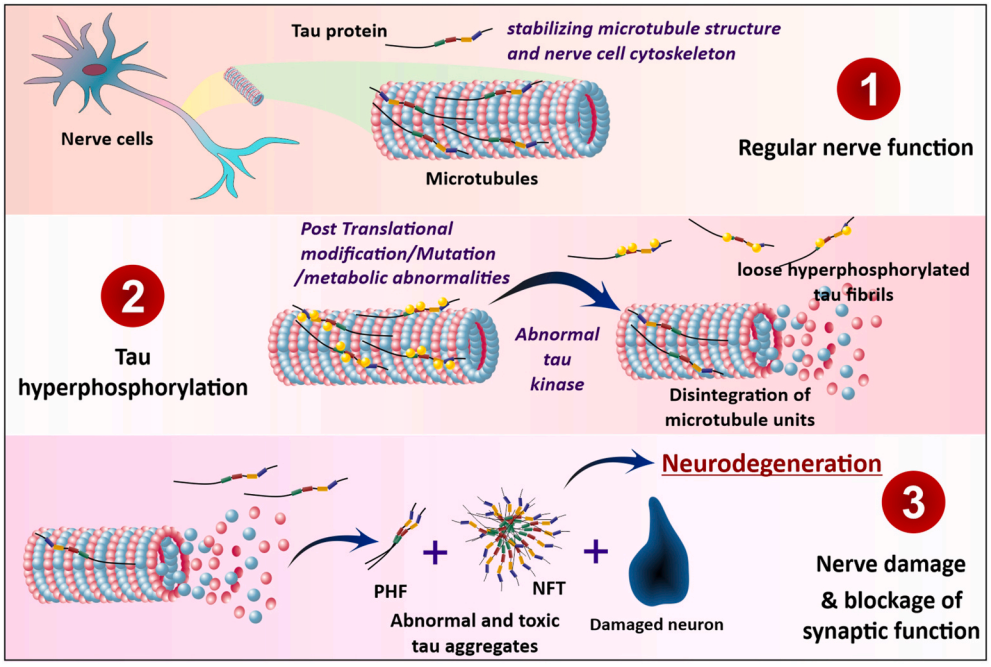

Fig. 2. Neurodegeneration by tau hyperphosphorylation (1) In a healthy brain, tau-protein stabilizes the microtubule assembly by holding tubulin sheets together through its isomers and phosphorylation. Hence, they maintain the nerve cell cytoskeleton and assist the regular function of neurons. (2) Post-translational modification, genetic mutation or any metabolic abnormalities cause hyperphosphorylation of tau protein which interfere with its function and tau fibrils detached from the microtubule. (3) This causes dissembling of microtubule units and ultimately neuronal death. The loosened tau fibrils form abnormal toxic aggregates (PHF and NFTs), which block the synaptic transport and lead to neurodegenerative diseases like AD.

inflammatory cytokines cause severe neuroinflammation. At the same time, Aβ aggregates synergistically act with cytokines to activate microglial cells. It interacts with glial cells via CD36-TLR4-TLR6 receptor complex and neuroinflammatory complex, leading to damage or death of the nerve cells, release TNF-α or other inflammatory mediators, and activate immune response. The significant increase of cytokines like TGF-β, IL-1β, IL-12, IL-18 etc. and TGF-α level in the brain increases neuronal damage and AD progression (Michaud et al., 2013). Conversely, a B-cell receptor, CD-22, exerts a negative impact on phagocytosis and causes a functional decline of microglia. Suppression of CD-22 facilitates the clearance of various fibrils, deposits and debris like Aβ fibrils from the brain, which could be a suitable strategy to lessen the inflammation and AD progression (Pluvinage et al., 2019).

3. Biomaterials

Biomaterials are referred as substances of either natural or synthetic origin, specially designed to interact with the living tissues in the form of medical devices, carrier system, diagnostic tools or other supporting materials used to treat, diagnose, repair, augment or replace the

damaged or diseased organ or tissue of the body except for food and drugs. Technological advancement in drug development and the medicinal industry increases the demand for smart biomaterials to manage critical conditions and access delicate organs in a better and convenient manner (Hadavi and Poot, 2016). These are also beneficial in drug delivery to the brain due to their unique abilities like excellent permeability, better solubility, flexible physicochemical properties, targeting specificity, biodegradability, biocompatibility, lesser toxicity, controlled and sustained release, stimuli responsiveness and many more. BBB appears a foremost challenge for brain targeting of therapeutic and diagnostic agents. Thus, various biomaterials are used as permeation enhancers, surface-active ligands, carrier molecules (protein, peptide etc.), and surface-modified nanocarriers to promote the drug passage across the BBB through passive transport, receptor-mediated and carrier-mediated transport. Nano vectors are a promising strategy for brain delivery of bioactives due to their smaller size and higher permeability across the BBB. Surface modification with specific ligands like transferrin, lactoferrin, glutathione etc., facilitates the entry of drugs to the brain via active transport mechanism through receptor or carrier-mediated transport. Smart biomaterials serve as an essential part of novel drug delivery to treat neurological disorders like Alzheimer's disease (Orive et al., 2009). The selection of appropriate biomaterial purely depends upon its characteristic features and compatibility with the therapeutic or diagnostic agent. And the physicochemical and mechanical properties of any biomaterial are based on its origin and structural composition. So, based on origin, biomaterials can be broadly divided into two categories, as discussed below.

3.1. Natural biomaterials

Various monomers, dimers, oligomers and polymers originated from natural sources like plants, animals, microorganisms, and marine species come under this category. These are the essential components of life, including amino acids, protein, peptide, lipids, carbohydrates (mono, oligo and polysaccharides), nitrogenous bases, nucleic acids etc. (Avinash and Govindaraju, 2018). Random and sequential rearrangement and organization of the basic units result in various fascinating macromolecules. Due to their special features like biocompatibility, biodegradability, flexibility, low toxicity etc., such compounds have variable application in the drug delivery system. Naturally originated biomaterials could be used to satisfy different aspects of drug delivery system ranging from the bioactives with therapeutic activities including various herbal extracts, proteins, peptides etc. to numerous polymers with permeation enhancing, release modifying, surface modifying properties to achieve target-specific treatment of AD and other CNS disorders more (Datta et al., 2020). The biomolecule-derived biomaterials, or naturally occurring biomaterials, offer great advantages in terms of biocompatibility, biodegradability, flexibility and safety over the synthetic biomaterials. Owing to the natural origin, they mostly mimic the biological or physiological environment and provide an attractive option over synthetic biomaterials. Although, the availability of standard quality materials, lower shelf-life and higher susceptibility to environmental and microbial degradation and immunogenicity might limit their application. However, advanced derivatives of natural biomaterials, either in combination with other synthetic or natural compounds or implementation of advanced technologies, overcome such limitations. Starch, fibrin, gelatin, collagen, alginate and their derivatives, various gums, resins, bioactive protein and peptides, different lipids like lecithin, phosphatidylcholine and phospholipids (from multiple sources like egg, soybean etc.), polysaccharides etc. are popular biomaterials used in drug delivery approaches among which chitosan, hyaluronic acid, phospholipids, wheat germ agglutinin, vegetable oils etc. found useful in brain delivery of bioactives (Song et al., 2018).

3.2. Synthetic biomaterials

Apart from the excellent biocompatibility and ability to support the cell functions, natural biomaterials are somewhat restricted due to lack of stability or higher tendency to degrade, and potency to carry microbial contamination evoke an immune response. On the other hand, synthetic biomaterials or synthetic derivatives of natural biomaterials offer better flexibility, mechanical strength and chemical properties. Synthetic polymers can be easily modified to alter their chemical and mechanical behavior to achieve desirable characteristics like stability, elasticity, bioadhesion etc. However, it possesses some other challenges like toxicity upon long-term usage (Fournier et al., 2003). Thus, to avoid such complications, various biodegradable synthetic biomaterials are being extensively studied for their biomedical applications. It is also possible to control and predict the physical and mechanical properties of synthetic biomaterials like rate of degradation, elastic modulus, tensile strength, etc., due to the well-understood and controlled production of these materials. Further, the quality and purity can also be controlled as per the need (Austin and Rosales, 2019). In all, the pure, biodegradable synthetic biomaterials are found suitable in combination with the natural biomaterials for therapeutic and diagnostic purposes owing to their minimum toxicity, higher stability and flexibility. Some common synthetic biomaterials involve the use of saturated aliphatic polyesters like PGA,[21] PLA,[22] PLGA,[23] PCL[24] etc., polyanhydrides, polyurethane, polyphosphazene etc. among which PLGA, PCL, PEG[25] are commonly used for brain delivery of bioactives and formulation of novel drug carriers (Song et al., 2018).

4. Role of functional biomaterials in AD therapy

Functional biomaterials are smart polymers which have the ability to demonstrate desired characteristics in response to any external stimulus like temperature, light, pH, magnetic field, electric stimulus etc., upon exposure to the physiological system (Wells et al., 2019). These are also termed as stimuli-responsive or smart biomaterials. There are primarily two types of stimulus based on its source of origin, including (i) endogenous stimulus and (ii) exogenous stimulus. The former involves physiological temperature, pH, ROS,[26] enzymes, ionic concentration and redox reactions. In contrast, the latter involves light, external temperature, magnetic field, ultrasound waves, and electric stimulus to trigger or activate these smart biomaterials (Rao et al., 2018). Smart biomaterials present an exquisite and evolutionary approach to provide optimized patient-centric care in terms of target-specific and on-demand therapy, which seems to be the prime lacuna in the conventional system. In AD therapy, endogenous stimulus-responsive materials are mostly explored for therapeutic purposes, i.e., to deliver the drug cargo to the affected region of the brain as a novel carrier system. On the contrary, endogenous biomaterials have been explored for diagnostic purposes as marker compounds or labeling agents (Shan et al., 2019). This section has highlighted the most recent application of some highly explored categories of smart biomaterials to treat AD.

4.1. pH-responsive biomaterials

pH-responsive functional biomaterials possess the ability to respond to the change in environmental pH and thus, provide release of drug package to the desired site or pathological conditions like amyloid aggregates, tumor tissues, site of inflammation etc. The pH-responsive

[21] Polyglycolic acid.
[22] Polylactic acid.
[23] Poly-lactide-co-glycolide.
[24] Polycaprolactone.
[25] Polyethylene glycol.
[26] Reactive oxygen species.

delivery system limits the systemic exposure of anti-AD drugs and enhances drug concentration at the damaged region of the brain with pH lower than general circulation. The acidic environment of the amyloid plaque, NFT,[27] damaged nerve cells or inflamed neurons regulates the drug release from this carrier or drug at the target site by triggering the physical or chemical changes. These are derivatives of polyelectrolytic polymers with weak acid or base in their backbone. The difference in surrounding pH promotes chemical or physical changes like cleavage of bonds, structural modification, change in solubility, swellability, proton release, or acceptance (Wells et al., 2019). Various natural polymers like chitosan, cellulose, albumin and gelatin demonstrate both pH and thermoresponsive behavior. At the same time, synthetic biomaterials like PEG, PAA[28] and PDMAEMA[29]/PDEAEMA[30] and their derivatives like Carbopol® (a crosslinked derivative of PAA) show pH-responsive behavior. Among this chitosan, PEG and PAA derivatives like Carbopol® are frequently explored to develop novel carriers to deliver anti-AD drugs (Chatterjee and Chi-Leung Hui, 2019). Gao et al. studied the effect of GMC[31] modified chitosan on the nasal absorption of insulin in the AD rat model at varying pH (Gao et al., 2019). Studies proved that insulin resistance and impaired insulin signaling act as a key factors for cognitive dysfunction and pathogenesis of neurodegenerative diseases like AD. Nasal administration of insulin potentially delays the AD progression and improves brain functions along with diabetes management (de la Monte, 2013; Dubey et al., 2020). The change in pH significantly influences the solubility of insulin and chitosan to promote drug absorption. It also leverages the electrostatic interaction between the bioactive (insulin) and chitosan). The study reported GMC-chitosan and insulin interaction at 5.8 and 6.7 pH results in encapsulation of insulin within the polymeric matrix while no/little interaction at 4.7 pH (Gao et al., 2019).

4.2. Thermoresponsive biomaterial

Thermoresponsive/thermosensitive or temperature-triggered biomaterials exhibit physical or chemical modification in response to change in the surrounding temperature. This ability has been used to achieve targeted drug delivery at the diseased site (inflamed tissues, Aβ[32] aggregates or other damaged tissues of the brain) with increased physiological temperature. This phenomenon can also ease the drug administration process via intranasal route, peroral administration or parenteral administration in a solution form, which gets converted to gel or depot after administration at physiological pH to produce a prolonged release of the drug (Agrawal et al., 2020a). Poloxamer, chitosan, EHEC,[33] xyloglucan, PNIPAM[34] etc., are some popular thermoresponsive biomaterials investigated for brain delivery of bioactives. A recent investigation explored the photothermic behavior of ruthenium nanoparticles to improve the permeability across BBB and provide a thermoresponsive release of NGF.[35] The study highlighted the development of a hollow, flower-like ruthenium nanoparticle loaded with NGF and modified with a phase-changing material, tetradecyl alcohol, to support the thermoresponsiveness. NGF is an effective neurotrophin which lessens nerve damage by inhibiting tau hyperphosphorylation and improves memory and learning functions. However, poor BBB permeability and a shorter half-life reduce its therapeutic efficacy (Zhou et al., 2020). The thermoresponsive release behavior of the developed nanocarrier prolonged the blood circulation time and prevented the early release of the drug. Excellent photothermal sensitivity under NIR[36] irradiation promotes its ability to improve the BBB permeability and smartly controlled NGF release under the thermal stimulus (Chen et al., 2017). In all, it effectively suppressed the multiple factors of AD pathogenesis, including tau hyperphosphorylation, oxidative stress and neuronal damage (Zhou et al., 2020). Georgieva et al. demonstrated the thermoresponsive behavior of PNIPAM for transdermal delivery of galantamine (a well-known anti-AD drug) to treat AD. Different polymeric network films were prepared, evaluated and loaded with galantamine. PNIPAM based formulation offers excellent thermoresponsive behavior to assist the transdermal administration of the drug in avoiding its systemic exposure and, thus, the adverse effects (Georgieva et al., 2020). Another study reported the amyloid targeting ability of a thermoresponsive novel conjugated polymer-based micelle to treat AD. The smart polymer consists of two PEG analogs, PMO[37] and POEG,[38] which exhibits excellent thermoresponsiveness and overcome the limitations of PNIPAM like poor mechanical strength, slow response, and low biocompatibility. The thermal stimulus triggers the polymeric conjugate transformation from hydrophilic to hydrophobic form, which further captures the Aβ fibril and prevents toxic Aβ plaque formation (Geng et al., 2020).

4.3. Photosensitive biomaterials

Light is an exogenous stimulus used to regulate the physiochemical and biological properties of the polymeric system to fulfill the therapeutic need. Light offers an inexpensive and flexible tool to control the movement inside the biological system, the release pattern and thus, achieve target-specific action. In the nervous system, the INS[39] can also be used to induce the excitation or suppression of neuronal activity (Martino et al., 2015). Considering the photo-stimulation in regulating neurological responses, photoactive biomaterials serve as a potential tool to target specific and better therapeutic action. The photoactive biomaterials are subdivided into photothermal, fluorescent, or optical waveguided biomaterials based on their different photo stimuli. The first category, the photothermal biomaterials demonstrates the ability to liberate thermal energy upon activation through the light stimulus. This thermal energy further triggers the physical, chemical or mechanical modification of the biomaterial to get the desired release behavior, target specificity, removal of protein aggregates or damaged cells and stimulate the surrounding tissues (Shan et al., 2019). In this sequence, Li et al. studied the light-controlled release behavior of PPy[40] nanoparticle-containing microscopic hydrogel loaded with a neurotransmitter triggered by NIR irradiation. The NIR stimulated photosensitive microgels were developed to provide the localized release of bioactives to control various neuronal activities in *in vivo* and *in vitro* models. The photothermal biomaterial was a combination of PNIPAM hydrogel and PPy nanoparticles. The PNIPAM exerts thermoresponsive behavior, and PPy serves as a photothermal transducer. The remote-controlled localized glutamate delivery induced by NIR irradiation stimulus demonstrated improved auditory cortex activity in the AD rat model (Li et al., 2015).

4.4. Electroresponsive biomaterials

Studies reported that electro-active cells like neurons and cardiac cells have the ability to generate an endogenous electric field in the form

[27] Neurofibrillary tangles.
[28] Polyacrylic acid.
[29] Poly(dimethylaminoethyl methacrylate).
[30] Poly(diethylaminoethyl methacrylate).
[31] Glyceryl monocaprylate.
[32] Amyloid beta.
[33] Ethyl (Hydroxyethyl) Cellulose.
[34] poly(N-isopropylacrylamide).
[35] Nerve Growth Factor.
[36] Near Infrared.
[37] poly-2-(2-methoxy ethoxy)-ethyl methacrylate-co-oligo(ethylene glycol) methacrylate.
[38] polyoligo(ethylene glycol) methacrylates.
[39] Infrared neural stimulation.
[40] Polypyrrole.

of specific cell membrane potential, which flows throughout the biological system as nerve impulses to transfer and carry the signals and cardiac impulses in the cardiovascular system. This electric potential typically ranges between −60 mV and −100 mV. In the human body, these endogenous electric impulses are essential to regulate various biological functions like nerve signaling, muscle contraction, tissue regeneration, embryogenesis, wound healing etc. It acts as an integral part of signal transmission and other nervous system functions like Transmission of action potential and depolarization (Li and Hoffman-Kim, 2008). Owing to this unique electrical attribute, the exogenous electric impulses also significantly impact nerve functioning. Thus, various electroactive biomaterials have been explored for their ability to modulate the cellular functions, the stimuli-controlled release of bioactives, detection and identification of biochemical reactions and neurotransmitters and photoacoustic imaging (Manivasagan et al., 2017). PANI,[41] PEDOT[42] and PPy are examples of conductive biomaterials, highly explored for nerve tissue regeneration and mitigation of neurological ailments. However, the non-biodegradability of these conductive polymers, which calls for surgical removal, is the primary obstruction in the *in vivo* application of these biomaterials. Thus, researchers focused on the synthesis of biodegradable conductive polymers. In this aspect, a study highlighted the fabrication of nerve ducts with a combination of PPy and PDLLA[43] to treat the defective nerves and promote neuroregeneration. The biodegradable PPy/PDLLA composite neuro conduit facilitated the rat PC-12 cell differentiation in the *in vitro* model and nerve regeneration in the rat model. Such ability of PPy/PDLLA composite could be further utilized in the AD brain to repair damaged neurons and facilitate neuroregeneration (Xu et al., 2014). Another example of biodegradable conductive biomaterial was the synthesis of biodegradable polyurethane by combining poly (glycerol sebacate) and aniline pentamer by polycondensation. The system potentially repaired the nerve damage and promoted nerve regeneration (Wu et al., 2016).

4.5. Magnetically controlled biomaterials

Magnetism is an inherent characteristic of every atom. Hemoglobin found in human blood, a protein with iron content, demonstrates magnetic behavior. The magnetic property of hemoglobin varies with its oxygen-carrying capacity. The oxygenated hemoglobin was less sensitive to the magnetic field than the deoxygenated one (Bren et al., 2015). Based on these facts, magnetic biomaterials were found to have significant importance in biomedical science. The magnetic biomaterials are used to design and synthesize magnetic nanoparticles for the controlled and target-specific delivery of various therapeutic and diagnostic agents. Pure metals like Fe, Co, Ni, Ti etc., metal oxides, ferrite, maghemite and metal alloys containing one of the above-mentioned metals are common magnetic biomaterials (Majidi et al., 2016). Iron oxide nanoparticle is popular in the biomedical industry for drug targeting or diagnosis owing to its lower toxicity profile. The magnetic IONs[44] are highly susceptible to the external magnetic field and lose their magnetization upon removing the external magnetic field (Dragar et al., 2021). This phenomenon is called superparamagnetism, which is highly desirable for the biomedical application of IONs. Usually, the IONs with a size below 20 nm possess such ability and termed as SPIONs[45] (Cardoso et al., 2018). Although the particle size should not be less than 10 nm is easily susceptible to rapid renal clearance. Decoration of SPIONs with target-specific biomaterial and combination with biocompatible and biodegradable agents improves its efficiency, site-specificity and compatibility with the biological system. The SPIONs were found useful in AD imaging as ultrasensitive nanoprobe. For this, the SPION was surface-functionalized with a carboxyl derivative of DDNP[46] through ligand exchange technique. DDNP is a viscosity and solvent sensitive, highly lipophilic, fluorescent compound with high affinity to Aβ aggregate. Hence, it was used as a molecular imaging probe to target senile plaque. The 11.7 nm sized magnetic nanoparticle showed significant binding to the Aβ aggregate in an *in vitro* Aβ model when visualized through fluorescent imaging. Excellent Aβ binding and fluorescent properties of DDNP and magnetically regulated SPION serve as potential diagnostic tools for AD. Such findings supported SPION's application as an MRI contrast agent for AD diagnosis (Zhou et al., 2014). It also has applications in stem cells targeting the hippocampal region of the brain to treat AD. The study demonstrated the labeling of Human WJ-MSCs[47] with dextran-coated SPIONs targeted to the hippocampus of the rat brain by applying the external magnetic field using the Halbach magnet array. The study reported improved memory and cognitive function, which assures the successful targeting of MSCs through SPIONs and its regenerative effects (Hour et al., 2020).

5. Biomaterial for development of novel carrier for brain targeting of anti-AD drugs

The unique characteristics of various natural and synthetic biomaterials have been used to design different types of novel drug carrier systems to target anti-AD drugs to the desired site of the brain. Here, we discuss the applications of biomaterial for the development of some well-known drug carriers, including polymeric nanoparticles, lipidic nanocarrier, inorganic nanoparticles, hydrogel, biodegradable scaffold, and carbon nanotube etc.

5.1. Polymer-based carrier systems

Polymer drug carriers received significant attention in novel drug delivery approaches in the past two decades. The unique properties of natural or synthetic polymers as biomaterials assist the drug delivery process with various advantages over the conventional system. Biodegradability, biocompatibility, flexibility, site-specificity, controlled release behavior, permeation enhancement, improved stability, less toxicity etc., are the most desirable characteristics of a polymeric carrier system. These can be used as a vector for delivering a broad range of bioactives, including synthetic drugs, herbal moieties, proteins, peptides, biological agents, gene and genetic factors, along with various diagnostic agents (Sung and Kim, 2020). Based on their inherent properties, method of preparation and structure of the final product, the polymeric biomaterials can be formed as polymeric nanoparticles, polymer-drug conjugates, micelles, polyplexes, dendrimers, etc. Surface modification of a polymer-based drug carrier with a targeting ligand gives precise targeting. This section will discuss the role of various biomaterials in developing a suitable carrier system for delivering bioactives to treat AD (Table 1).

5.1.1. Polymeric nanoparticles

The field of nanotechnology had some drastic evolutions in the past years to produce potential drug delivery systems capable of imposing minimum toxicity. The materials with a size of 1–100 nm were preferable for nanosize formulation (Alexander et al., 2016). In Alzheimer's condition, when the patient is administered with these nanoparticles, there are number of evidence that they may promote, suppress, or delay the kinetics of amyloid plaque formation. Apart from the above advantage, the polymeric nanoparticles also have some limitations like the accumulation of biomaterials in the brain, non-biodegradability,

[41] polyaniline.
[42] poly(3,4-ethylene dioxythiophene).
[43] Poly(D,L-lactic acid).
[44] Iron oxide nanoparticles.
[45] Superparamagnetic iron oxide nanoparticle.
[46] 1,1-dicyano-2-[6-(dimethylamino)naphthalene-2-yl]propene.
[47] Wharton's jelly-derived mesenchymal stem cells.

Table 1
Some examples of biomaterials used as therapeutic agents and development of polymer-based carrier system.

S. no.	Targeted Pathological factor	Bioactives/Drug	Biomaterials	Outcome	References
Polymeric nanoparticles					
	Oxidative stress	Lutein	PLGA	• 17.64% after 6 h & up to 71% was released in 96 h • Erosion controlled sustained release of lutein from polymeric matrix • Higher permeation to nasal mucosa • Lesser cellular toxicity • Bioavailability is more through intra-nasal route	Dhas and Mehta (2020)
	AChE	Alendronate sodium	Chitosan, Sodium tripolyphosphate	• Prolonged and controlled release • Around 88.61% of drug released in 24 h • Improved spatial memory in mice due to synergistic effect of chitosan and the drug • Effective brain targeting due to high affinity to hippocampal neurons	Zameer et al. (2020)
	Aβ aggregation	Curcumin	Selenium	• Sustained release of drug from selenium matrix up to 24 h • New targeting agents for AD is selenium nanoparticles • Selenium increases bioavailability as a penetration enhancer	Huo et al. (2019)
	Aβ aggregation	anti-$A\beta_{1\text{-}42}$ monoclonal antibody	PEG derivatives	• Monoclonal antibodies can treat memory loss in AD • Long circulation half-life was due to PEGylation	Carradori et al. (2018)
	Aβ fibrillogenesis	Insulin	Maghemite	• Increase therapeutic potency • Better brain targeting	Lu et al. (2018)
Dendrimers					
	AChE	Tacrine	PAMAM	• Complexation with PAMAM dendrimer does not alter drug release, which shows weak interaction • Decreases toxicity • Increased drug efficacy	Igartúa et al. (2020)
	NMDA excitotoxicity & glutamate overexpression	Memantine	PAMAM	• Initial burst release for 1 h followed by slow and sustained release of 51.23% in 48 h • Increased permeability • No memory deficits in mice	Gothwal et al. (2019)
	Protein aggregation due to impaired autophagy	Carbamazepine	PAMAM	• Initial burst release with subsequent sustained release • PAMAM dendrimer enhances drug solubility • Reduced toxicity • Higher bioavailability	Igartúa et al. (2018)
	Inflammatory damage & γ-secretase irregularity	Flurbiprofen	poly (epsilon-lysine)	• High permeability • Less cytotoxicity	Al-Azzawi et al. (2018)
Micelle					
	Oxidative stress	Resveratrol	PEG-PLA	• NCAM is efeective target for AD	Yang et al. (2020)
	Oxidative stress & inflammatory damage	–	lactoferrin and conjugated linoleic acid	• 11% in 2 h and approximately 100% in subsequent 8 h at 6.8 pH • Safe and effective treatment • 2.8 fold increase in *in-vivo* distribution	Agwa et al. (2020)
	Aβ aggregation, oxidative stress & inflammatory damage	Curcumin	DSPE-PEG_{2000}	• Reduction in Aβ plaque • Early diagnosis of AD • High accumulation in brain tissues	Chibhabha et al. (2020)
	Aβ aggregation, oxidative stress & inflammatory damage	RAGE targeting peptide, Curcumin	PEG polymer, which has ROS responsiveness	• Multi-targeting • Increase in cellular uptake	Lu et al. (2019)

systemic toxicity in some conditions (Dhas and Mehta, 2020). Thus, numerous efforts have been made to design promising polymeric nanoparticles with desirable properties. One such strategy highlighted the role of cationic chitosan functionalized PLGA core/shell nanoparticles for brain delivery of carotenoid (lutein) through the intranasal route to treat AD. Lutein is a natural dietary xanthophyll carotenoid, identified as an anti-AD drug due to its potential anti-inflammatory and antioxidant activity. However, poor solubility and bioavailability restricted its therapeutic potency. Hence, it was embedded in PLGA nanoparticles to improve solubility and bioavailability and achieve brain targeting. PLGA nanoparticle was prepared by nanoprecipitation method. The system was then coated with chitosan by electrostatic interaction. The prepared nanoparticles had particle size, PDI,[48] and zeta potential 134–145 nm, 0.01, and +48 mV, respectively. The release of lutein from the nanoparticles was sustained after 8 h up to 96 h. The electrostatic interactions between endothelial cells and cationic chitosan-coated nanoparticles lead to the internalization of the nanocarriers. The chitosan-coated lutein-PLGA nanoparticles had a great ability to cross the nasomucosal membrane and effectively deliver the drug cargo to the brain, where lutein exerts therapeutic action by reducing the oxidative stress in nerve cells (Dhas and Mehta, 2020). Another study also demonstrated the use of chitosan nanoparticles for nose-to-brain delivery of alendronate. Alendronate is a nitrogenous bisphosphonate with the potency to inhibit the AChE and cholesterol synthesis. The drug was encapsulated with chitosan by ionic gelation technique, using sodium tripolyphosphate as a crosslinking agent. The carrier provides sustained release of a drug where the initial burst release was less than 39% in 30 min. The permeation rate of the formulation was more than expected due to the interaction of the amino acid group with the negatively charged cell surface. The chitosan nanoparticle promisingly delivers the drug to the brain via the intranasal route and provides an effective, non-invasive technique to treat AD (Alexander et al., 2014; Zameer et al., 2020). PLGA nanoparticles are

[48] Polydispersity index.

extensively investigated for the brain delivery of a broad range of therapeutics, including small hydrophilic molecules, lipophilic drugs, proteins, peptides and various other macromolecules (Ferreira et al., 2020). Utilizing this strategy, Huo et al. developed selenium nanoparticle doped PLGA nanospheres for effective brain targeting of curcumin. The work aimed to enhance the cellular uptake and transport of this poorly soluble drug across BBB to treat AD. The curcumin-loaded selenium-PLGA nanosphere was prepared using the emulsion solvent evaporation method, which produces a nanosphere with a size of approximately 80 nm. The initial burst release of selenium-loaded curcumin-PLGA nanoparticles was less compared to curcumin-PLGA loaded nanoparticles. Selenium increased the BBB penetration and also exerted a synergistic effect with curcumin to treat neuronal damage. The formulation significantly reduces Aβ aggregation and neuroinflammation in 5XFDA transgenic AD mice (Huo et al., 2019). PEG is one of the very popular biomaterials used in developing novel carrier systems for brain delivery. Its unique features are used to get desirable characteristics like stealth nature, biocompatibility, prolonged-release, reduce toxicity, improve permeability and surface modification of nanoparticles to protect the therapeutics and target-specific delivery. The fate of PEG inside the body depends on its molecular weight (Ajazuddin et al., 2013). Various derivatives of PEG are used in nanoformulations to improve bioavailability and efficiency. Using the PEG derivatives Carradori et al. developed antibody (anti-A$\beta_{1\text{-}42}$) functionalized PEGylated polymeric nanoparticle and investigated its fate in the *in vivo* transgenic AD mice model towards AD treatment. Treatment of transgenic mice with antibody decorated nanocarrier showed considerable improvement in memory and reduced the Aβ level in the brain (Carradori et al., 2018) (Table 1).

5.1.2. Dendrimer

Another popular polymeric carrier is dendrimer, which has gained popularity to access the brain in the last decade. Dendrimers are novel drug carriers with tree-like structures where branches are formed from the core molecule in hierarchical order. Various advantages of dendrimers like high density, monodispersity, controllable size and a high degree of surface functionality make them suitable for site-specific drug delivery. Different types of dendrimers have been synthesized based on composite biomaterials like PAMAM,[49] PPI[50], carbosilane, PLL,[51] and triazine. PAMAM is the most common and acceptable polymer for biomedical applications due to its biocompatibility, flexibility, and low cost (Igartúa et al., 2018). Igartua et al. reported co-administration of tacrine, a licensed anti-AD drug with PAMAM dendrimer, to minimize the toxicity profile and improve the therapeutic efficacy of the drug. They prepared a suspension of tacrine and dendrimers (DG 4.0 and 4.5) in methanol and studied the interaction. The toxicological profile was evaluated using human RBC[52] for *ex vivo* toxicity, cell culture studies (Neuro-2a cell culture) to determine the *in vitro* toxicity and zebrafish larvae for *in vivo* toxicity. The study revealed a significant decrease in cell viability when treated with 300 μM of tacrine. In contrast, no sign of toxicity was observed when tacrine was administered along with 1.8 μM of DG 4.0 or 4.5 (Igartúa et al., 2020). Previously, they have utilized PAMAM dendrimer for brain delivery of carbamazepine to improve drug solubility, reduce dose, dosing frequency, adverse effect, and therapy cost. Complexation with PAMAM dendrimer significantly increases the solubility of the drug, almost 3 folds. At the same time, the formulation was also found to be safe in *ex vivo* human blood cell, *in vitro* N2a cell and *in vivo* zebrafish model (Igartúa et al., 2018). Another similar work evaluated the brain targeting efficiency of Lf[53] conjugated PAMAM dendrimer for delivering memantine (NMDA antagonist) through *in vivo* AD mouse model. ^{1}HNMR confirmed the Lf-PAMAM conjugation by chemical reaction. Conjugation with Lf significantly increases the size of the drug-loaded PAMAM dendrimer from 11.5 to 131.7 nm. The cationic behavior of the lactoferrin increases the zeta potential, and surface coating with Lf slows down the drug release rate and provides sustained release as desired. The Lf conjugated dendrimer successfully delivered the drug to the brain with improved bioavailability and showed improvement in memory and behavioral function of AD mouse model (Gothwal et al., 2019). Another exciting piece of work demonstrated the use of PEL[54] dendrimer for brain delivery of flurbiprofen, a USFDA approved anti-inflammatory drug to treat AD. The dendrons were initially prepared by solid-phase peptide synthesis and coupled with flurbiprofen. The binding of the polymer and drug was confirmed using mass spectroscopy and FTIR analysis. The cell viability of the formulation was performed on bEnd.3 cells, and the system was found highly biocompatible. Drug integration with the PEL dendrimer increased permeation across BBB and delivered the drug to the target site by hydrolysis. The formulation effectively targeted the drug to the desired site on the γ-secretase enzyme (Al-Azzawi et al., 2018) (Table 1).

5.1.3. Micelles

Polymeric micelles are nanosized carriers with core-shell arrangements formed by spontaneous self-association of amphiphilic block copolymers in an aqueous solution. The micelle structure has a hydrophilic shell and hydrophobic core, enabling the entrapment of hydrophobic molecules in the core and entrapment of hydrophilic moieties in the shell (Shah and Leon, 2021). Such an arrangement makes it compatible with a wide variety of both hydrophobic and hydrophilic drugs. The size of the micelles can be adjusted based on the requirement. It offers a great advantage of surface modification with target active ligands, enabling drug delivery to the target site by minimizing the off-site delivery (Agwa et al., 2020). Oxidative stress and mitochondrial dysfunctioning are well-accepted causative factors of AD. Effective targeting of potent antioxidants to the neurons could be a promising way to mitigate the oxidative stress-induced mitochondrial dysfunction and slow down the disease progression. Using this strategy, Yang et al. developed neuronal mitochondria targeting polymeric micelle, co-decorated with C3 (neuron adhesion molecule mimicking peptide) and TPP[55] to target mitochondria. Resveratrol was entrapped in PEG-PLA-based micelles, which are then functionalized on the surface with C3 and TPP. The TPP-modified particles can escape lysosomal enzymes and facilitates localization in mitochondria. The formulation attenuates the oxidative stress-induced mitochondrial damage, restored the cognitive functions in APP[56]/PS1[57] transgenic mice model, alleviates tau hyperphosphorylation and amyloid deposition and protects the synapses (Yang et al., 2020). Additionally, micelles can increase the solubility of the drug and enhance biocompatibility. One such work was reported by Chibhabha et al., where they developed DSPE-PEG_{2000} micelles with curcumin by the solvent evaporation method. The encapsulation efficiency was less than 79%, while the drug loading capacity was less than 14% with 80–100 nm particle diameter. The sensitivity of the micelles to Aβ plaque was predicted by immunofluorescence imaging of APP_{SWE}/PSIΔE9 mice brain and retinal sections, which showed a significant reduction of Aβ plaque. The toxicity of the formulation was minimum in both ARPE-19 and 661W retinal cell lines (Chibhabha et al., 2020) (Table 1).

[49] polyamidoamine.
[50] polypropylene-imine.
[51] poly-L-lysine.
[52] Red blood cells.
[53] Lactoferrin.
[54] Poly(epsilon lysine).
[55] Triphenylphosphonium.
[56] Amyloid precursor protein.
[57] Presenilin 1.

5.2. Lipid-based carrier system

Another important class of biomaterials is natural or synthetic lipids or lipophilic substances used to develop an interesting class of nanocarriers, lipid nanoparticles. Nowadays, lipid-based drug carriers have gained much popularity compared to the other nanocarrier systems owing to the great advantage of biocompatibility, biodegradability, and less toxicity than polymeric and inorganic materials, and better permeation through various biological membranes, higher drug loading and many more. Approximately 70% of the nanomedicines in clinical trials up to 2019 were formulated using lipids as their carrier. Phospholipids are more biocompatible and can self-assemble into lipid-based carriers better than other polymeric or inorganic materials. Different types of lipid nanoparticles are formulated and defined on the basis of their composition, structure, method of preparation and other formulation variables (Fan et al., 2021). Here, we have discussed some most recent strategies highlighting the application of lipid nanocarriers for brain targeting of bioactives to treat AD (Table 2).

5.2.1. Liposome

Liposome is one of the highly explored nanocarriers for AD therapy. It is a nano-sized lipophilic vesicle composed of a phospholipid bilayer surrounding an aqueous core. Such a special arrangement of liposome with lipophilic shell and aqueous core permits the loading of hydrophilic drug in the core and hydrophobic moieties in the phospholipid shell (Agrawal et al., 2018). It is a non-toxic, biocompatible carrier system that significantly improves the solubility, permeability and bioavailability of the drug and potentially targets it to the desired site. Apart from such advantages, poor stability is a significant limitation of the liposomal delivery system, which can be overcome using suitable stabilizers (Antimisiaris et al., 2021). Liposome is susceptible to RES[58] when administered through the IV[59] route and undergoes cellular metabolism and clearance. Thus, to protect it from physiological degradation, various surface modification has been done. One such strategy is PEGylation or stealth liposome, which circumvent the RES clearance, improves the circulation time, and facilitates drug targeting to the brain (Bruch et al., 2019). One recent strategy on PEGylated liposomes reported the development of transferrin-modified osthole loaded liposomes by thin-film hydration method. The prepared liposomes were then PEGylated with PEG_{2000}/DSPE-PEG_{2000}. The fluorescence intensity of cells with PEGylated liposomes was 1.61 times more than other cells, which shows more uptake of the liposomes by cells. The neuroprotective effect of the liposomes was analysed using APP–SH–SY5Y cells, and the viability was more than 80%. *In vivo* pharmacokinetics and biodistribution studies revealed that PEGylation prolonged the circulation time and transferrin facilitated brain targeting (Kong et al., 2020). The same drug osthole, is used to target CXCR-4[60], on which the sole ligand present was SDF-1 highly expressed in Alzheimer's, reported by Ni et al. The CXCR-4 modified osthole liposomes were prepared by thin-film hydration, with a particle size of less than 110 nm and zeta potential −11 mV. The liposomes prepared increased the cell viability of cells and exert a protective effect. The targeting of liposomes was evaluated by making a placebo preparation, and the liposomes still entered inside the brain of mice. It was then proven that the liposomes effectively target the SDF-1 in the brain (Ni et al., 2020). Saffari et al. reported the co-administration of metformin and phosphatidylserine liposomes as neuroprotective agents to ameliorate AD pathologies like memory deficit and neuroinflammation. The prepared nanoliposomes have a particle size of 150 nm and 39% encapsulation efficiency. The formulation effectively targeted the brain and improves memory and learning ability in AD-rat, decreases cytokine level, neuroinflammation and neuronal necrosis (Saffari et al., 2020) (Table 2).

5.2.2. Nanoemulsion

Nanoemulsion is thermodynamically stable isotropic mixtures of two immiscible liquids, one organic and another aqueous phase stabilized with suitable surfactants and co-surfactants (Thomas et al., 2017). The average size of the nanoemulsion globule is 10–200 nm. The oil droplets can hold lipophilic drugs, while the aqueous phase holds the hydrophilic drugs. This formulation enhances the drug solubility, mucosal permeability, dissolution rate, and overall bioavailability. It is a non-toxic, non-irritating, highly biocompatible and stable drug carrier system that can be formulated as a variety of semisolid and liquid dosage forms like cream, gel, spray, foam, drops etc. Kaur et al. studied brain targeting efficiency of donepezil loaded o/w nanoemulsion administered through the intranasal route. The nanoemulsion was prepared by homogenization of Labrasol, cetyl pyridinium chloride and glycerol. The globule size of the nanoemulsion was 65.3 nm with zeta potential −10.7 mV. The cell viability was done on Neuro 2a cell lines, and it showed the viability of 77%. The formulation was stable up to 24 h and was safe on nerve cells. It demonstrated improved uptake by brain cells, dose-dependent cytotoxicity and antioxidant activity (Kaur et al., 2020). Also, Jiang et al. reported brain delivery of Huperzine A loaded lactoferrin conjugated nanoemulsion via the intranasal route. *In vitro* study revealed uptake by CMEC/D3 cells was higher than unmodified nanoemulsion. The mechanism of drug transport was predicted as receptor-mediated transcytosis, which proved lactoferrin efficiency for brain targeting. Better pharmacokinetic and animal study data also supported the hypothesis that intranasal nanoemulsion is a potential tool to target the AD site (Jiang et al., 2019) (Table 2).

5.2.3. SLN

SLN is the new generation delivery system containing solid lipid as the main core and biocompatible surfactant as an outer shell. Some of the unique characteristics of the use of SLN are its high drug loading capacity, small size, higher effective surface area, better stability than other lipid carriers, biocompatibility, compatibility with a broad range of therapeutics, and minimum toxicity profile, solubility and permeability enhancement. Owing to the properties mentioned above, SLN offers a promising carrier for brain targeting. SLN is mostly preferred for delivering proteins, peptides, and other considerable molecular weight hydrophobic drugs and suitable for all the other classes of bioactives. These are currently highly explored for developing novel therapies to treat various neurological disorders like AD (Agrawal et al., 2020b). One such study by Satya et al. reported the brain targeting of a natural antioxidant and neuroprotective agent α-Bisabolol to alleviate Aβ aggregation and mitigate neurotoxicity. SLN was prepared by a hot homogenization method using soy lecithin, tween 80 and cholesterol. α-Bisabolol has a higher affinity to the lipid matrix, increasing the drug encapsulation and minimizing the loss during the encapsulation process. The system considerably reduces the activity of AChE, oxidative stress and thereby diminished neurotoxicity and Aβ aggregation (Sathya et al., 2020). Another similar example is the brain delivery of andrographolide, a diterpenoid through SLN, to get neuroprotective and antioxidant effects. Graverini et al. prepared andrographolide loaded SLN by emulsification method with compritol 888 ATO, Brij 78. The burst release from the carrier is due to the drug-enriched lipid shell. The permeability of andrographolide into the cells was enhanced due to its formulation into nanocarriers. When the formulation was administered to rats, there is no microglia activation, which indicates that brain macrophages do not consider the SLN as foreign bodies. The results showed that SLN significantly increased the drug's bioavailability and brain targeting (Graverini et al., 2018). Another natural product incorporated into SLN was Resveratrol. This was reported by Yadav et al. using lecithin, taurocholate, stearic acid. The *in vitro* release showed biphasic release with initial burst release due to the three hydroxyl

[58] Reticuloendothelial system.
[59] Intravenous.
[60] chemokine receptor 4.

Table 2
Some examples of biomaterials used as therapeutic agents and development of lipid-based carrier system.

S. no.	Targeted Pathological factor	Bioactives/Drug	Biomaterial	Outcome	References
Liposomes					
	ApoE expression & amyloid plaque	Osthole	Transferrin	• pH-controlled release up to 72 h • Enhanced penetration • High therapeutic efficacy	Kong et al. (2020)
	Oxidative stress & neuroinflammation	Osthole	CXCR 4	• Sustained release of 70% drug in 72 h • Effectively target SDF-1 part of the brain	Ni et al. (2020)
	Neuroinflammation	Metformin	Phosphatidylserine	• Decreased neuroinflammation	Saffari et al. (2020)
	Aβ aggregation	Apoprotein E2	Transferrin	• Targets BBB through gene therapy	Dos Santos Rodrigues et al. (2019)
Nanoemulsion					
	Cholinergic dysfunctioning	Donepezil	Labrosol (oil phase), cetyl pyridinium chloride (surfactant), glycerol (co-surfactant)	• 96% burst release in 2h in PBS media • Enhanced activity • High cell viability	Kaur et al. (2020)
	Cholinergic dysfunctioning	Huperzine A	Capryol 90 (oil phase), Cremophor EL & Labrasol (surfactant & co-surfactant) & Lactoferrin (targeting ligand)	• Showed sustained release with less than 85% release in 24 h • Lactoferrin is used to target BBB • High activity	Jiang et al. (2019)
	Aβ aggregation	Naringenin	–	• More activity than free drug • Has potent action	Md et al. (2018)
SLN					
	Neuroinflammation	Erythropoietin	EPO, glyceryl monostearate	• Initial burst release of 41.02% in 3 h followed by sustained release of 83.22% in next 21 h • Minimum cytotoxicity at BBB cell line • Potentially delivers protein to the brain	Dara et al. (2019)
	Aβ aggregation	α-Bisabolol	Soy lecithin	• Initial burst release of 17% in 2 h with subsequent slow and sustained release of 98% in 128 h • Impact on neuroprotective potential	Sathya et al. (2018)
	Oxidative stress and neuroinflammation	Andrographolide	Compritol 888 ATO, Brij 78	• Burst release in first 6 h followed by sustained release • Increased bioavailability • Enhanced efficacy	Graverini et al. (2018)
	Oxidative stress and neuroinflammation	Resveratrol	Lecithin	• Sustained-release with 91.0% after 24 h • Effective in treating oxidative stress • More bioavailability in the brain	Yadav et al. (2018)
NLC					
	Oxidative stress and neuroinflammation	Quercetin	Cetyl palmitate and miglyol-812	• Effective in crossing BBB • Inhibits amyloid-beta aggregation	Pinheiro et al. (2020)
	Cholinergic dysfunctioning	Rivastigmine	Glyceryl distearate and phosphatidylcholine	• 60% at 12 h and 89% at 48 h • Alternate approach for delivering drugs through nose to brain delivery	Cunha et al. (2020)
	Cholinergic dysfunctioning	Rivastigmine	Castor oil and glyceryl monostearate	• Treats dementia in AD	Chauhan and Sharma (2019)
	Cholinergic dysfunctioning	Donepezil hydrochloride	Stearic acid, oleic acid, lecithin, and sodium taurodeoxycholate	• Burst release at 12 h followed by sustained release • Enhanced penetration of drug • Enhanced activity	Mendes et al. (2019)

groups present in the structure, localized in the core and interface near the shell. The bioavailability in the brain was 4.5 times higher than free drugs. The drug can diminish oxidative stress and cognitive defects, and this action was done by activating the Nrf2/HO-1 pathway. This shows that the formulation effectively alleviated oxidative stress and cognitive impairments (Yadav et al., 2018) (Table 2).

5.2.4. NLC

Nanocarriers enhance the delivery of drugs to the target site. SLN and NLC are very similar types of nanocarriers with some distinct characteristics. NLC is one such nanocarrier composed of solid and liquid lipids, where SLN consists of only solid lipids. It is also known as the second generation SLN. NLC is composed of a blend of solid and liquid lipid stabilized by surfactant coating. The boon is its higher loading capacity due to the imperfect arrangement of solid lipid crystals, excellent stability, non-immunogenicity and biocompatibility. Due to their colloidal nature, they can easily penetrate through the skin and other physiological membranes, making them a potential carrier to access the tough regions of the body like the brain. The site-specific delivery of the NLC was investigated by Pinheiro et al. in comparison with SLN. The quercetin-loaded NLC was prepared by hot homogenization with cetyl palmitate as solid lipid and miglyol-812 as liquid lipid with transferrin as targeting ligand. The study reported, NLC had higher entrapment efficiency than SLN. Cell permeability studies were done on hCMEC/D3 cells, and again NLC showed better cellular permeability. However, excessive exposure of cellular receptors to the transferrin leads to saturation and restricts the drug uptake after a threshold limit. The prepared formulation satisfactorily inhibits amyloid fibrillation in the brain than SLN. The nanosystem effectively crosses BBB and exerts high Aβ plaque inhibition activity (Pinheiro et al., 2020). Direct nose-to-brain delivery of NLC is a fascinating and popular strategy in the past few years. It offers higher brain targeting and minimum adverse effect due to less systemic exposure. Cunha et al. developed rivastigmine-loaded NLC with glyceryl di-stearate and phosphatidylcholine by high-pressure homogenization using this approach. The prepared NLC formulations are an alternative and effective drug delivery approach through the nose to brain route. The study focused on formulation optimization by the QbD approach (Cunha et al., 2020).

NLC also possesses higher permeability across the skin due to its lipophilic nature. This unique feature of NLC could make it suitable for transdermal delivery of bioactives to the brain as an alternative approach to omit systemic exposure. Utilizing a similar approach, Chauhan et al. designed rivastigmine-loaded castor oil and glyceryl monostearate based NLC by the HPH[61] method. The NLC significantly enhances the drug bioavailability in the brain, which was maintained upon loading into the transdermal patch. Hence, it can effectively manage dementia (Chauhan and Sharma, 2019) (Table 2).

5.3. Inorganic carrier system

Inorganic nanoparticles elicited considerable interest because of their enthralling physicochemical properties, smaller size and stability. Quantum dots, gold, silver, mesoporous silica, magnetic nanoparticles etc., have been broadly used for diagnosis and imaging of many acute and chronic disorders. Their unique electrical, chemical, and magnetic capabilities make them highly competent for imaging and diagnosis. Inorganic nanoparticles possess high photostability compared to high photobleaching in fluorophores (Alexander et al., 2019a). Summary of various inorganic biomaterials used for brain targeting as drug delivery vehicles or diagnostic agents are given in Table 3.

5.3.1. Quantum dots

Quantum dots are semiconductor particles fall in the range of nanometer size. It exhibits distinct electronic and optical characteristics owing to the quantum mechanics, which varies with the size and composition of the nanoparticle. These nanocrystals are considered as artificial atoms with a size range between 2 and 10 nm diameters. It is composed of a core-shell type structure where the semiconductor fluorescent materials are enveloped within an outer shell of another semiconductor (Alexander et al., 2019b; Yuan et al., 2021). Novel materials like these have distinguished electro-optical capabilities like high QY,[62] symmetrical and sharp emission peaks, photoluminescence, photobleaching resistance, and the ability for multicolor fluorescence under a single-wave excitation. It offers efficient and tunable photoluminescence with excellent photochemical stability (Cotta, 2020). Inorganic quantum dots are known to be structurally more stable than organic quantum dots and hence possess good shelf lives. Novel tools like an innovative fluorescent probe, quantum dots distinguish themselves in unique size, chemical stability, and spectral properties compared with the historic dyes used in fluorescence studies (Galstyan, 2021). One of the most studied form is graphene quantum dots which offers good electrochemical properties. The graphene quantum dots not only enhanced their electrochemical properties but also imparted fluorescence sensitivity. Hence, present a dual-sensing platform for detecting ApoE4-biomarker by using EDC/NHS chemistry for bioconjugation with a DNA probe. The probe was amino terminated with CM-GQD[63]-ITO[64] system using malonic acid as a spacer. The modification of graphene quantum dots on ITO electrode helped in improving the electron transfer rate. When incubated with various concentrations of ApoE4 DNA, the amperometric measurements decreased with increase in the concentration of ApoE4 and reduces the electron transfer capability of curcumin (Ruther et al., 2013). GQD as a biomaterial is not only limited to diagnostics but also extensively explored as a novel carrier for drug delivery. These are known to be having appreciable solubility, flexible surface properties, small size, and are economical with no toxicity *in vivo* and *in vitro*. The availability of epoxy/ether, –CO–NH_2, C═O, and –OH surface functional groups enable their use as a biomaterial for the development of drug delivery systems with multiple functions. They can minimize the cytotoxic effects of the Aβ oligomer by inhibiting the aggregation of $A\beta_{1\text{-}42}$. Neuroprotective peptides like GPE[65] can be conjugated with GQD and the Aβ inhibition activity was tested on APP/PS1 transgenic mice. The formulation showed good inhibitory effect on $A\beta_{1\text{-}42}$ fibrils in the brain and serum resulting in improved learning and memory capacity *in vivo* (Xiao et al., 2016) (Table 3).

5.3.2. Magnetic nanoparticle

The majority of the available magnetic nanoparticles have proven to be nontoxic and possess good absorption capabilities for decades. SPIONs have been explored as theranostics for various neurodegenerative disorders, including AD. These are widely employed as contrast agents for MRI[66] and nano-drug carriers for AD and can assist in detecting early hall markers, protein aggregates of AD pathogenesis. Gd^{3+}[67] chelates have been successfully inducted in imaging of Aβ plaque using high-field MRI (Wahsner et al., 2019). SPIONs is structurally composed of ferric and ferrous ion core with an outer coating of dextran or other polysaccharide. These are having relatively good chemical stability, high saturation magnetic moment, and minimal toxicity (Jarockyte et al., 2016). SPIONs have been widely utilized as a membrane shell material to prepare magnetic nanobubbles for boosted ultrasound MRI dual contrast imaging and cellular fate tracking of loaded cargoes *in vivo* due to their exceptional chemical, physical, and biological properties (Thanh and Green, 2010). Release control, monitoring the drug distribution, and targeting the desired site are major challenges in AD therapy, significantly affecting drug efficacy and toxicity. Hence, there is a need for promising delivery systems for site-specific, controlled delivery of therapeutic and diagnostic agents. In this view, the use of siRNA as gene therapy to repair genetic defects opened new perspectives in AD treatment. Utilizing this, a distinguished work has been reported by Lopez-Barbosa and coworkers; they prepared a PEGylated magnetite nanoparticle to deliver immobilized siRNA. The siRNA was modified at 3′ and 5′ end with thiol group to suppress the expression of the BACE1 gene, responsible for Aβ accumulation. Furthermore, a translocation protein OmpA was co-immobilized on the prepared magnetite nanoparticles. The PEGylation of the magnetite nanoparticles conferred the stealth property and increased their solubility and biocompatibility. The co-immobilization of OmpA translocation protein facilitated the cellular internalization and significantly enhanced the endosomal escaping property of the prepared vehicle for siRNA strand without affecting its biocompatibility. The developed PEGylated magnetite nanoparticle significantly suppressed the BACE1 gene expression in HFF-1 human fibroblast cell lines. The cell viability was more than 82%. After 7 days, endosomal escape efficiency in SH-SY5Y human neuroblastoma cell lines were 69% and 89% for PEGylated nanoparticles and OmpA/PEGylated nanoparticles, respectively. Hence, these multifunctional magnetite nanoparticles could be employed as an efficient vehicle to deliver siRNA to the targeted site to manage AD pathogenesis (Lopez-Barbosa et al., 2020). Distinctly, magnetic nanoparticles also serve as potential diagnostic tools and carriers to deliver suitable analytes for early and precise diagnosis of AD and precise diagnosis of AD. In a relevant work, multifunctional SPION was prepared by surface conjugation with scFv[68] antibody W20 and XD4.[69] The system was aimed to detect AβO[70] as a potential biomarker for early diagnosis of AD. W20-SPION provides a safer way to target AβO without inducing any inflammatory reaction. Alongside, XD4 facilitates microglial phagocytosis of AβO by activating class A scavenger receptors. SPION assures brain targeting of this molecular MRI probe to the brain. In all, the

[61] High pressure homogenization.
[62] Quantum Yield.
[63] Graphene quantum dots.
[64] Indium tin oxide.
[65] Glycine-proline-glutamate.
[66] Magnetic resonance imaging.
[67] Gadolinium.
[68] Single chain variable fragment.
[69] Scavenger receptor activator.
[70] Amyloid β oligomer.

Table 3
Some examples of biomaterials used as therapeutic agents and development of inorganic and other nanocarrier systems.

S. no.	Targeted Pathological factor	Bioactive	Biomarker/ Analyte	Biomaterial	Outcome	References
Quantum Dots						
	Genetic factor-ApoE4	Curcumin	ApoE4 DNA	Graphene quantum dots & Indium–Tin-Oxide Electrode	• LOD of fluorescence sensing has been estimated to be 12.4 ng/mL • High sensitivity towards detection of ApoE4 DNA	Mars et al. (2018)
	Amyloid plaque	Streptavidin	$A\beta_{1-42}$	CdSe–ZnS	• The linear range of Aβ1–42 assay is from 5.0 to 100 pM (0.023–0.45 ng/mL) and LOD 1.7 pM (7.6 pg/mL)	Tang et al. (2018)
	Amyloid plaque & inflammation	Glycine-Proline-Glutamate (GPE) peptide	–	Graphene	• Inhibited Aβ aggregation • Improved memory and learning in APP/PS1 transgenic mice • Reduced pro-inflammatory cytokine level in the brain of experimental animal	Xiao et al. (2016)
	–	–	ApoE	CdSe–ZnS quantum dots & PDMS[a]-PC[b] microfluidic chip	• Potentially detect ApoE as biomarker for AD • LOD value of 12.5 ng/mL	Medina-Sánchez et al. (2014)
Magnetic Nanoparticles						
	–	Neural stem cells	–	SPION enclosed nanobubbles	• Stable structure • Significant contrast enhancement in Ultrasound imaging (US) and MRI • Potential nanocarrier for US/MRI dual model imaging	Li et al. (2020)
	APP accumulation	siRNA	–	Magnetite	• Immobilization of siRNA maintains biological activity • Silencing of BACE1 gene in HFF-1 cells	Lopez-Barbosa et al. (2020)
	Amyloid aggregation	–	AβO	W20/XD4-SPION	• Promote microglial phagocytosis of AβO • Early detection of AD biomarker • Safer mode of brain targeting of diagnostic tool	Liu et al. (2020)
	Cholinergic dysfunction, Cognitive decline, neuroinflammation	Human Wharton's Jelly derived MSCs	–	Dextran coated SPION	• Successfully target the MSCs to the hippocampal region of AD rat • Improved cholinergic functions of hippocampal cells • Memory and cognitive improvement	
Gold Nanoparticles						
	Tau hyperphosphorylation	Cab-GA conjugate	Tau protein & immunocomplex	Electrografted PABA	• Effectively detect tau protein as AD biomarker from human blood plasma and brain homogenate • LOD value of 1.7 pg/mL • More effective to diagnose AD	Razzino et al. (2020)
	Amyloid aggregation	L and D glutathione	–	Gold nanoparticles	• Effective to cross BBB • Rescue memory deficits in AD	Hou et al. (2020)
	Amyloid aggregation	Bucladesine	–	Gold nanoparticles	• Effective in relieving memory impairment and neuronal damage • Redirection of Aβ peptide fibrillation kinetics	Sanati et al. (2019)
OTHER NOVEL CARRIER SYSTEMS						
Hydrogels						
	Cholinergic dysfunction	Donepezil hydrochloride	–	PVA-PVP Hydrogel	• Enhanced mechanical and pharmacokinetic properties • Effective delivery of donepezil via transdermal route	Bashyal et al. (2020)
	Amyloid aggregation	–	–	Collagen type I based 3D hydrogel system	• Significant confinement of Aβ • Low cytotoxicity	Simpson et al. (2020)
	APP accumulation & amyloidogenesis	Resveratrol	–	Gellan gum and xanthan gum-based *in situ* gelling system	• 5-6-fold increase in penetration of drug • Improved memory and cognitive function of an AD rat model	Rajput et al. (2018)
	Amyloid aggregation, oxidative stress & neuroinflammation	Curcumin	–	Neuro-compatible peptide-based hydrogel	• On enzymatic degradation gives neuropeptide • Significant neuroprotection	Adak et al. (2017)
Biodegradable Scaffolds						

(*continued on next page*)

Table 3 (*continued*)

S. no.	Targeted Pathological factor	Bioactive	Biomarker/ Analyte	Biomaterial	Outcome	References
	Cholinergic dysfunction	2-furoyl piperazine derivatives	–	Medicinal scaffold for enzyme inhibition	• Superior inhibitory action on BChE	Hassan et al. (2019)
	Cholinergic dysfunction	Coumarin & lipoic acid	–	Coumarin-Lipoic acid conjugated scaffolds	• Significant inhibition of self-induced and AChE-induced Aβ1-42 aggregation	Jalili-Baleh et al. (2018)
	Cholinergic dysfunction, Amyloid aggregation & oxidative stress	Triazolopyrimidine quinoline & cyanopyridinequinoline	–	Scaffold	• Selective inhibition of AChE • Promising neuroprotective effect	Kumar et al. (2016)

[a] Polydimethylsiloxane.
[b] Polycarbonate.

developed W20/XD4-SPION presented a highly selective and sensitive diagnostic tool for the early detection of AD (Liu et al., 2020). The magnetic nanoparticles were also found effective in the targeted delivery of human Wharton's jelly derived MSCs[71] to the hippocampus of the AD rat model. The developed system offered a potential regenerative medicine for AD treatment. It was found to improve the cognitive functions of the brain, reduce neuroinflammation and enhance functions of cholinergic neurons (Hour et al., 2020). All these studies have established the use of magnetic nanoparticles for targeted drug delivery, contrast enhancement for both US and MRI, and tracking of cellular fate on a long span in Alzheimer's disease management (Table 3).

5.3.3. Gold nanoparticles

Gold nanoparticles or GNPs[72] are well known for fascinating physicochemical attributes owing to their morphological and optical properties. The availability of superficial electrons allows them to resonate when stimulated with the incident light, known as SPR.[73] GNPs can absorb energy from a light source and proficiently scatter it as heat energy and produce light scattering. Notably, this light scattering property is capable of enhancing the fluorescence emission of nearby fluorescent molecules present at an optimum vicinity to the gold surface. This capability of GNPs has been employed in various studies involving the detection of biomarkers *in vitro* by SEF[74] (Kaushal et al., 2020). GNR[75] has been developed for fluorescence-based detection (using CRANAD-2 fluorescent probe) and therapeutic intervention (using D1 peptide) of Aβ accumulation. CRANAD-2 is a derivative of curcumin with a great affinity for insoluble amyloids like Aβ fibrils. It can give good fluorescence emission in the NIR region and useful for *in vivo* applications. Also, D1 is an **endogenous protease** resistant peptide formed using D amino acids and can restrict the aggregation of Aβ and encourage Aβ disaggregation. The functionalization of D1 peptide in the presence of CRANAD-2 with GNR significantly improved the fluorescence intensity signal of CRANAD-2 for *in vitro* and *ex vivo* (Jara-Guajardo et al., 2020). Tau protein is another biomarker for AD and is considered more accurate for predicting disease severity. The soluble pre-filaments are the most toxic and significant tau aggregates responsible for AD pathology. Razzino and coworkers fabricated disposable SPCEs[76] and used gold nanoparticles- PAMAM nanocomposites to modify the fabricated SPCEs (3D-Au-PAMAM) for the sandwich immunoassay and amperometry-based detection of tau proteins in human plasma samples and brain tissues. The use of gold nanoparticle encapsulated PAMAM dendrimer here imparted $-NH_2$ surface functional group, excellent biocompatibility, and conductivity. 3D-Au-PAMAM was covalently bonded with ρ-ABA.[77] The system further immobilizes the CAb[78] by crosslinking with GA[79] of the developed 3D-Au-PA-MAM-ρ-ABA. The resultant immunosensor and horseradish peroxidase labeled detector antibodies were used to sandwich the tau protein and detect the immunocomplex. This gold nanoparticle-based immunosensor detected tau protein levels in human plasma and tissue extracts with improved LOD of 1.8 pg/mL and excellent selectivity in AD patients (Razzino et al., 2020). Glutathione has both D and L chiral forms, which have been recognized to protect tissue damage resulting from ROS and potentially be used in AD therapeutics. The abundant presence of glutathione transporters in the brain makes them a good surface capping agent for Gold nanoparticles, enabling the GNPs to permeate through BBB. Notably, this surface chirality and helix structure of L- and D-glutathione can enantio-selectively prevent Aβ aggregation *in vitro* (Guan et al., 2018). In a similar study, Sanati and co-workers demonstrated the neuroprotective property of bare gold nanoparticles in rat models treated through intrahippocampal and intraperitoneal routes. The GNPs showed significant improvement in acquisition and retention of spatial learning and memory along with the good indication of neuronal survival evaluated by expression of various brain-derived neurotrophic factors (BDNF[80]) stromal interaction molecules, cAMP[81] binding protein, binding protein, and stromal interaction molecules like STIM1 and STIM2 (Sanati et al., 2019) (Table 3).

5.4. Other novel carrier systems

Novel carrier systems like hydrogels, biodegradable scaffolds, stimuli-responsive systems, and carbon nanotubes can be inducted for developing efficient treatment strategies for brain-related disorders like AD. They have the ability to overcome various limitations faced by conventional delivery systems, like low bioavailability, non-biocompatibility, and non-specificity to the target. Additionally, novel drug carriers can actively cross the BBB and efficiently deliver the cargoes into the lesion site and overcome the poor bio-integration seen in conventional delivery systems for cell replacement therapy in neurological disorders (Table 3).

5.4.1. Hydrogel

Among the various biomaterials used, hydrogels offer significant advantages because of their exceptional biodegradability, biocompatibility, and reactivity properties. These are composed of a network like cross-linked soft materials in a 3D structure capable of retaining a considerable volume of aqueous fluids or water (Chai et al., 2017). Based on molecular interaction present, they can be classified into chemical hydrogels and physical hydrogels. The chemical hydrogels have covalent bonding, whereas the physical hydrogels comprise hydrogen bonding, hydrophobic interactions, and ionic cross-linking

[71] Mesenchymal stem cells.
[72] Gold nanoparticles.
[73] Surface Plasmon Resonance.
[74] Surface-Enhanced Fluorescence.
[75] Gold Nano Rods.
[76] Screen 3D printed carbon electrodes.
[77] ρ-aminobenzoic acid.
[78] anti-tau capture antibody.
[79] Glutaraldehyde.
[80] brain-derived neurotrophic factors.
[81] Cyclic adenosine monophosphate.

(Lim et al., 2019). Broadly hydrogels show efficient loading capacity for both small and large cargo molecules, additionally, due to their similarity with normal tissues concerning physiological activity, they can be employed to load and diffuse nutrient levels below normal biological conditions. Synthetic or natural materials like cellulose, PEG, PVA,[82] hyaluronic acid, sodium alginate, chitosan, PVP,[83] gelatin methacrylate, casein, other modified electroconductive polymers can be used to prepare hydrogels for multipurpose applications (Tian et al., 2020). In line with cell-based treatments, the 3D structure of hydrogels can be used for enclosing various types of cells. Additionally, hydrogels in a pre-gel state can be implanted in the brain directly for delayed *in situ* gelations facilitating localization of graft and implanted cells into the cortical and subcortical regions. Polymers of a mixture of components/blends can be used to prepare hydrogels by submerging them in an aqueous solution forming an insoluble 3D gel state with tunable water content along with gelation and degradation time. Hydrogels prepared from chitosan, silk fibroin, methylcellulose, Matrigel, PLGA-PEG, hyaluronan, isopropyl acrylamide have been used particularly for cell/drug delivery applications into CNS (Fernandez-Serra et al., 2020). The PG[84]-hydrogel patch significantly improved the bioavailability of donepezil *in vivo* in hairless rats. Along with an excellent pharmacokinetic profile, the system also provides a dose-dependent reduction of AD symptoms as a feature of hydrogel-mediated permeation (Bashyal et al., 2020). In contrast to 2D-based cell culture techniques for developing AD drugs, 3D hydrogel culture significantly improves AD therapeutics by restricting Aβ cytotoxicity responsible for neurodegeneration. Rat tail collagen type I based 3D hydrogel system with 2D based cell culture system was evaluated for Aβ detection and lessening cytotoxic effects. The 3D environment provided by the hydrogel system can efficiently reduce the cytotoxicity of PC12 cell lines by reducing the susceptibility towards Aβ, likely by altering the diffusivity of Aβ into the 3D hydrogel system and varying the Aβ aggregation (Simpson et al., 2020). The nanostructured *in situ* hydrogel system can be developed using the melt emulsification-probe sonication method for the delivery of resveratrol through nasal mucosa to treat AD. Gellan gum and xanthan gum were employed to induce *in situ* gelations by incorporated NLC. The prepared *in situ* gel significantly enhanced resveratrol permeation by five to six folds with respect to conventional suspension across sheep nasal mucosa. Additionally, the NLC incorporated *in situ* gel prolongs the adhesion time with nasal mucosa and provides effective treatment for AD (Rajput et al., 2018). The various work discussed here shows a great potential of hydrogel-based systems in preventing neurodegeneration and the management of AD (Table 3).

5.4.2. Biodegradable scaffold

In the past decade, significant efforts have been made to synthesize functionalized biodegradable biomaterials that can be used as a scaffold for developing regenerative medicine (Guo et al., 2015). Scaffold or extracellular matrix acts as a template for tissue regeneration and facilitates adhesion of cells, differentiation, proliferation, and formation of new tissues in three dimensions. Scaffold design should have a biocompatible and biodegradable substrate along with controlled degradation rates, a highly porous three-dimensional structure to facilitate cell adhesion, penetration, proliferation, and interconnected pores enabling nutrient and waste exchange. Along with these, the biodegradable scaffold should also have sufficient mechanical strength for backing regeneration (Nikolova and Chavali, 2019). In contrast to metal or ceramics-based scaffold, the biodegradable polymer offers the most widely used scaffolding material owing to its great flexibility in processing and biodegradability incorporated by molecular design (Liu et al., 2012). Hassan and coworkers designed a medicinal scaffold for enzyme inhibition-based treatment for Alzheimer's disease. BChE[85] has been associated with Aβ and is a promising target for AD treatment. Series of scaffolds were developed using 2-furoyl piperazine-based derivatives and evaluated for BChE inhibitory potential by *in vitro* and in silico studies (Hassan et al., 2019). Coumarin and lipoic acid conjugated scaffolds have been designed as multi-target-directed ligands for the effective treatment of AD. The designed scaffolds showed higher inhibition of self-induced and AChE-induced $A\beta_{1\text{-}42}$ aggregation with respect to the reference drug donepezil. Additionally, the reduction of intracellular ROS generation decreased ferric ion, and chelation of selective metal showed that the synthesized compound acts as an effective multifunctional antioxidant (Jalili-Baleh et al., 2018). All these various studies highlight the potential application of biodegradable scaffolds design for effective treatment of AD through a multitarget approach (Table 3).

6. Conclusion

Even with the plethora of investigational reports and literature on successful target-specific therapies using the unique features of numerous biomaterials, the fact is we still lack a proper cure for AD. Most of the research shows success in preclinical studies and fails to reproduce in different clinical trials. Although some of the strategies are under clinical trials, most of them fail to reproduce the desirable effects. Also, the strategies are still focusing on mitigating the symptoms of AD instead of the pathophysiological factors. Only a few target-acting moieties, gene therapy and nerve regeneration therapies give hope to treat the disease causative factor and remove it from the roots. However, these therapies are at their initial level and very difficult to scale up. Concerning the biomaterials, both the available and investigational diagnostic and therapeutic approaches utilized specific biomaterials to reach the brain in different forms. It assists drug permeation across BBB, protects the drug property, minimizes the side effect, targets the bioactive to the affected site, and ensures cost-effective therapy as per the need. Use as biosensor probe, MRI imaging agents and carrier for delivery of diagnostic agents showed another interesting mode of using biomaterials for effective diagnosis and management of AD. The combined application of suitable biomaterial with precise strategy and advanced technologies will undoubtedly result in promising diagnostic and therapeutic tool to treat AD in the near future.

CRediT authorship contribution statement

Mukta Agrawal: Conceptualization, Writing – review & editing. **Eluri Prathyusha:** Writing – original draft. **Hafiz Ahmed:** Writing – original draft. **Sunil Kumar Dubey:** Validation. **Prashant Kesharwani:** Writing – review & editing. **Gautam Singhvi:** Writing – review & editing. **V.G.M. Naidu:** Visualization. **Amit Alexander:** Visualization, Formal analysis, Supervision.

Declaration of competing interest

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

Acknowledgment

The author wants to acknowledge National Institute of Pharmaceutical Education and Research, Guwahati, India, to provide necessary support.

[82] Polyvinyl alcohol.
[83] Polyvinyl pyrrolidone.
[84] Propylene glycol.
[85] Butyrylcholinesterase.

References

Adak, A., Das, G., Barman, S., Mohapatra, S., Bhunia, D., Jana, B., Ghosh, S., 2017. Biodegradable neuro-compatible peptide hydrogel promotes neurite outgrowth, shows significant neuroprotection, and delivers anti-alzheimer drug. ACS Appl. Mater. Interfaces 9, 5067–5076.

Agrawal, M., Saraf, S., Saraf, S., Antimisiaris, S.G., Hamano, N., Li, S.D., Chougule, M., Shoyele, S.A., Gupta, U., Ajazuddin, Alexander, A., 2018. Recent advancements in the field of nanotechnology for the delivery of anti-Alzheimer drug in the brain region. Expet Opin. Drug Deliv. 15, 589–617.

Agrawal, M., Saraf, S., Saraf, S., Dubey, S.K., Puri, A., Gupta, U., Kesharwani, P., Ravichandiran, V., Kumar, P., Naidu, V.G.M., Murty, U.S., Ajazuddin, Alexander, A., 2020a. Stimuli-responsive in situ gelling system for nose-to-brain drug delivery. J. Contr. Release 327, 235–265.

Agrawal, M., Saraf, S., Saraf, S., Dubey, S.K., Puri, A., Patel, R.J., Ajazuddin, Ravichandiran, V., Murty, U.S., Alexander, A., 2020b. Recent strategies and advances in the fabrication of nano lipid carriers and their application towards brain targeting. J. Contr. Release 321, 372–415.

Agwa, M.M., Abdelmonsif, D.A., Khattab, S.N., Sabra, S., 2020. Self- assembled lactoferrin-conjugated linoleic acid micelles as an orally active targeted nanoplatform for Alzheimer's disease. Int. J. Biol. Macromol. 162, 246–261.

Ajazuddin, Alexander, A., Amarji, B., Kanaujia, P., 2013. Synthesis, characterization and in vitro studies of pegylated melphalan conjugates. Drug Dev. Ind. Pharm. 39, 1053–1062.

Al-Azzawi, S., Masheta, D., Guildford, A.L., Phillips, G., Santin, M., 2018. Dendrimeric poly(epsilon-lysine) delivery systems for the enhanced permeability of flurbiprofen across the blood-brain barrier in Alzheimer's disease. Int. J. Mol. Sci. 19.

Alexander, A., Agrawal, M., Uddin, A., Siddique, S., Shehata, A.M., Shaker, M.A., Ata Ur Rahman, S., Abdul, M.I.M., Shaker, M.A., 2019a. Recent expansions of novel strategies towards the drug targeting into the brain. Int. J. Nanomed. 14, 5895–5909.

Alexander, A., Ajazuddin, Patel, R.J., Saraf, S., Saraf, S., 2016. Recent expansion of pharmaceutical nanotechnologies and targeting strategies in the field of phytopharmaceuticals for the delivery of herbal extracts and bioactives. J. Contr. Release 241, 110–124.

Alexander, A., Ajazuddin, A., Khan, J., Saraf, S., Saraf, S., 2014. Formulation and evaluation of chitosan-based long-acting injectable hydrogel for PEGylated melphalan conjugate. J. Pharm. Pharmacol. 66, 1240–1250.

Alexander, A., Saraf, S., Saraf, S., Agrawal, M., Patel, R.J., Agrawal, P., Khan, J., Ajazuddin, 2019b. Amalgamation of stem cells with nanotechnology: a unique therapeutic approach. Curr. Stem Cell Res. Ther. 14, 83–92.

Antimisiaris, S.G., Marazioti, A., Kannavou, M., Natsaridis, E., Gkartziou, F., Kogkos, G., Mourtas, S., 2021. Overcoming barriers by local drug delivery with liposomes. Adv. Drug Deliv. Rev. https://doi.org/10.1016/j.addr.2021.01.019.

Austin, M.J., Rosales, A.M., 2019. Tunable biomaterials from synthetic, sequence-controlled polymers. Biomater Sci 7, 490–505.

Avinash, M.B., Govindaraju, T., 2018. Architectonics: design of molecular architecture for functional applications. Acc. Chem. Res. 51, 414–426.

Bashyal, S., Shin, C.Y., Hyun, S.M., Jang, S.W., Lee, S., 2020. Preparation, characterization, and in vivo pharmacokinetic evaluation of Polyvinyl alcohol and Polyvinyl pyrrolidone blended hydrogels for transdermal delivery of donepezil HCl. Pharmaceutics 12.

Bren, K.L., Eisenberg, R., Gray, H.B., 2015. Discovery of the magnetic behavior of hemoglobin: a beginning of bioinorganic chemistry. Proc. Natl. Acad. Sci. U. S. A. 112, 13123–13127.

Bruch, G.E., Fernandes, L.F., Bassi, B.L.T., Alves, M.T.R., Pereira, I.O., Frézard, F., Massensini, A.R., 2019. Liposomes for drug delivery in stroke. Brain Res. Bull. 152, 246–256.

Cardoso, V.F., Francesko, A., Ribeiro, C., Bañobre-López, M., Martins, P., Lanceros-Mendez, S., 2018. Advances in magnetic nanoparticles for biomedical applications. Adv Healthc Mater 7.

Carradori, D., Balducci, C., Re, F., Brambilla, D., Le Droumaguet, B., Flores, O., Gaudin, A., Mura, S., Forloni, G., Ordoñez-Gutierrez, L., Wandosell, F., Masserini, M., Couvreur, P., Nicolas, J., Andrieux, K., 2018. Antibody-functionalized polymer nanoparticle leading to memory recovery in Alzheimer's disease-like transgenic mouse model. Nanomed. Nanotechnol. Biol. Med. 14, 609–618.

Chai, Q., Jiao, Y., Yu, X., 2017. Hydrogels for biomedical applications: their characteristics and the mechanisms behind them. Gels 3.

Chatterjee, S., Chi-Leung Hui, P., 2019. Review of stimuli-responsive polymers in drug delivery and textile application. Molecules 24.

Chauhan, M.K., Sharma, P.K., 2019. Optimization and characterization of rivastigmine nanolipid carrier loaded transdermal patches for the treatment of dementia. Chem. Phys. Lipids 224, 104794.

Chen, G., Xu, M., Zhao, S., Sun, J., Yu, Q., Liu, J., 2017. Pompon-like RuNPs-based theranostic nanocarrier system with stable photoacoustic imaging characteristic for accurate tumor detection and efficient phototherapy guidance. ACS Appl. Mater. Interfaces 9, 33645–33659.

Chibhabha, F., Yang, Y., Ying, K., Jia, F., Zhang, Q., Ullah, S., Liang, Z., Xie, M., Li, F., 2020. Non-invasive optical imaging of retinal Aβ plaques using curcumin loaded polymeric micelles in APP(swe)/PS1(ΔE9) transgenic mice for the diagnosis of Alzheimer's disease. J. Mater. Chem. B 8, 7438–7452.

Cotta, M.A., 2020. Quantum dots and their applications: what lies ahead? ACS Applied Nano Materials 3, 4920–4924.

Cunha, S., Costa, C.P., Loureiro, J.A., Alves, J., Peixoto, A.F., Forbes, B., Sousa Lobo, J. M., Silva, A.C., 2020. Double optimization of rivastigmine-loaded nanostructured lipid carriers (NLC) for nose-to-brain delivery using the quality by design (QbD) approach: formulation variables and instrumental parameters. Pharmaceutics 12.

Dara, T., Vatanara, A., Nabi Meybodi, M., Vakilinezhad, M.A., Malvajerd, S.S., Vakhshiteh, F., Shamsian, A., Sharifzadeh, M., Kaghazian, H., Mosaddegh, M.H., 2019. Erythropoietin-loaded solid lipid nanoparticles: preparation, optimization, and in vivo evaluation. Colloids Surf. B Biointerfaces 178, 307–316.

Datta, L.P., Manchineella, S., Govindaraju, T., 2020. Biomolecules-derived biomaterials. Biomaterials 230, 119633.

de la Monte, S.M., 2013. Intranasal insulin therapy for cognitive impairment and neurodegeneration: current state of the art. Expet Opin. Drug Deliv. 10, 1699–1709.

Dhas, N., Mehta, T., 2020. Cationic biopolymer functionalized nanoparticles encapsulating lutein to attenuate oxidative stress in effective treatment of Alzheimer's disease: a non-invasive approach. Int J Pharm 586, 119553.

Di Meo, S., Reed, T.T., Venditti, P., Victor, V.M., 2016. Role of ROS and RNS sources in physiological and pathological conditions. Oxid Med Cell Longev, 1245049, 2016.

Dos Santos Rodrigues, B., Kanekiyo, T., Singh, J., 2019. ApoE-2 brain-targeted gene therapy through transferrin and penetratin tagged liposomal nanoparticles. Pharm. Res. (N. Y.) 36, 161.

Dragar, Č., Kralj, S., Kocbek, P., 2021. Bioevaluation methods for iron-oxide-based magnetic nanoparticles. Int. J. Pharm., 120348

Du, X., Wang, X., Geng, M., 2018. Alzheimer's disease hypothesis and related therapies. Transl. Neurodegener. 7, 2.

Dubey, S.K., Lakshmi, K.K., Krishna, K.V., Agrawal, M., Singhvi, G., Saha, R.N., Saraf, S., Saraf, S., Shukla, R., Alexander, A., 2020. Insulin mediated novel therapies for the treatment of Alzheimer's disease. Life Sci. 249, 117540.

Dubey, S.K., Ram, M.S., Krishna, K.V., Saha, R.N., Singhvi, G., Agrawal, M., Ajazuddin, SarafS., Saraf, S., Alexander, A., 2019. Recent expansions on cellular models to uncover the scientific barriers towards drug development for Alzheimer's disease. Cell. Mol. Neurobiol. 39, 181–209.

Fan, Y., Marioli, M., Zhang, K., 2021. Analytical characterization of liposomes and other lipid nanoparticles for drug delivery. J. Pharmaceut. Biomed. Anal. 192, 113642.

Fernandez-Serra, R., Gallego, R., Lozano, P., González-Nieto, D., 2020. Hydrogels for neuroprotection and functional rewiring: a new era for brain engineering. Neural Regen Res 15, 783–789.

Ferreira, N.N., Granja, S., Boni, F.I., Prezotti, F.G., Ferreira, L.M.B., Cury, B.S.F., Reis, R. M., Baltazar, F., Gremião, M.P.D., 2020. Modulating chitosan-PLGA nanoparticle properties to design a co-delivery platform for glioblastoma therapy intended for nose-to-brain route. Drug Deliv Transl Res 10, 1729–1747.

Fournier, E., Passirani, C., Montero-Menei, C.N., Benoit, J.P., 2003. Biocompatibility of implantable synthetic polymeric drug carriers: focus on brain biocompatibility. Biomaterials 24, 3311–3331.

Galstyan, V., 2021. "Quantum dots: perspectives in next-generation chemical gas sensors" – A review. Anal. Chim. Acta, 238192.

Gao, M., Sun, Y., Kou, Y., Shen, X., Huo, Y., Liu, C., Sun, Z., Zhang, X., Mao, S., 2019. Effect of glyceryl monocaprylate–modified chitosan on the intranasal absorption of insulin in rats. J. Pharmacol. Sci. 108, 3623–3629.

Geng, H., Yuan, H., Qiu, L., Gao, D., Cheng, Y., Xing, C., 2020. Inhibition and disaggregation of amyloid β protein fibrils through conjugated polymer-core thermoresponsive micelles. J. Mater. Chem. B 8, 10126–10135.

Georgieva, D., Ivanova-Mileva, K., Ivanova, S., Kostova, B., Rachev, D., Christova, D., 2020. Thermoresponsive poly(N-isopropylacrylamide) copolymer networks for galantamine hydrobromide delivery. Colloid Polym. Sci. 298, 377–384.

Gong, C.X., Iqbal, K., 2008. Hyperphosphorylation of microtubule-associated protein tau: a promising therapeutic target for Alzheimer disease. Curr. Med. Chem. 15, 2321–2328.

Gothwal, A., Kumar, H., Nakhate, K.T., Ajazuddin, Dutta, A., Borah, A., Gupta, U., 2019. Lactoferrin coupled lower generation PAMAM dendrimers for brain targeted delivery of memantine in aluminum-chloride-induced Alzheimer's disease in mice. Bioconjugate Chem. 30, 2573–2583.

Graverini, G., Piazzini, V., Landucci, E., Pantano, D., Nardiello, P., Casamenti, F., Pellegrini-Giampietro, D.E., Bilia, A.R., Bergonzi, M.C., 2018. Solid lipid nanoparticles for delivery of andrographolide across the blood-brain barrier: in vitro and in vivo evaluation. Colloids Surf. B Biointerfaces 161, 302–313.

Guan, Y., Du, Z., Gao, N., Cao, Y., Wang, X., Scott, P., Song, H., Ren, J., Qu, X., 2018. Stereochemistry and amyloid inhibition: asymmetric triplex metallohelices enantioselectively bind to Aβ peptide. Science Advances 4, eaao6718.

Guo, B., Lei, B., Li, P., Ma, P.X., 2015. Functionalized scaffolds to enhance tissue regeneration. Regen Biomater 2, 47–57.

Hadavi, D., Poot, A.A., 2016. Biomaterials for the treatment of Alzheimer's disease. Front Bioeng Biotechnol 4, 49.

Hampel, H., Vergallo, A., Caraci, F., Cuello, A.C., Lemercier, P., Vellas, B., Giudici, K.V., Baldacci, F., Hänisch, B., Haberkamp, M., Broich, K., Nisticò, R., Emanuele, E., Llavero, F., Zugaza, J.L., Lucía, A., Giacobini, E., Lista, S., 2020. Future avenues for Alzheimer's disease detection and therapy: liquid biopsy, intracellular signaling modulation, systems pharmacology drug discovery. Neuropharmacology, 108081.

Hassan, M., Abbasi, M.A., Aziz ur, R., Siddiqui, S.Z., Shahzadi, S., Raza, H., Hussain, G., Shah, S.A.A., Ashraf, M., Shahid, M., Seo, S.-Y., Malik, A., 2019. Designing of promising medicinal scaffolds for Alzheimer's disease through enzyme inhibition, lead optimization, molecular docking and dynamic simulation approaches. Bioorg. Chem. 91, 103138.

Hou, K., Zhao, J., Wang, H., Li, B., Li, K., Shi, X., Wan, K., Ai, J., Lv, J., Wang, D., Huang, Q., Wang, H., Cao, Q., Liu, S., Tang, Z., 2020. Chiral gold nanoparticles enantioselectively rescue memory deficits in a mouse model of Alzheimer's disease. Nat. Commun. 11, 4790.

Hour, F.Q., Moghadam, A.J., Shakeri-Zadeh, A., Bakhtiyari, M., Shabani, R., Mehdizadeh, M., 2020. Magnetic targeted delivery of the SPIONs-labeled

mesenchymal stem cells derived from human Wharton's jelly in Alzheimer's rat models. J. Contr. Release 321, 430–441.
Huo, X., Zhang, Y., Jin, X., Li, Y., Zhang, L., 2019. A novel synthesis of selenium nanoparticles encapsulated PLGA nanospheres with curcumin molecules for the inhibition of amyloid β aggregation in Alzheimer's disease. J. Photochem. Photobiol., B 190, 98–102.
Igartúa, D.E., Martinez, C.S., Del, V.A.S., Prieto, M.J., 2020. Combined therapy for Alzheimer's disease: tacrine and PAMAM dendrimers Co-administration reduces the side effects of the drug without modifying its activity. AAPS PharmSciTech 21, 110.
Igartúa, D.E., Martinez, C.S., Temprana, C.F., Alonso, S.D.V., Prieto, M.J., 2018. PAMAM dendrimers as a carbamazepine delivery system for neurodegenerative diseases: a biophysical and nanotoxicological characterization. Int J Pharm 544, 191–202.
Jalili-Baleh, L., Forootanfar, H., Küçükkılınç, T.T., Nadri, H., Abdolahi, Z., Ameri, A., Jafari, M., Ayazgok, B., Baeeri, M., Rahimifard, M., Abbas Bukhari, S.N., Abdollahi, M., Ganjali, M.R., Emami, S., Khoobi, M., Foroumadi, A., 2018. Design, synthesis and evaluation of novel multi-target-directed ligands for treatment of Alzheimer's disease based on coumarin and lipoic acid scaffolds. Eur. J. Med. Chem. 152, 600–614.
Jara-Guajardo, P., Cabrera, P., Celis, F., Soler, M., Berlanga, I., Parra-Muñoz, N., Acosta, G., Albericio, F., Guzman, F., Campos, M., Alvarez, A., Morales-Zavala, F., Kogan, M.J., 2020. Gold nanoparticles mediate improved detection of β-amyloid aggregates by fluorescence. Nanomaterials 10.
Jarockyte, G., Daugelaite, E., Stasys, M., Statkute, U., Poderys, V., Tseng, T.C., Hsu, S.H., Karabanovas, V., Rotomskis, R., 2016. Accumulation and toxicity of superparamagnetic iron oxide nanoparticles in cells and experimental animals. Int. J. Mol. Sci. 17.
Jiang, Y., Liu, C., Zhai, W., Zhuang, N., Han, T., Ding, Z., 2019. The optimization design of lactoferrin loaded HupA nanoemulsion for targeted drug transport via intranasal route. Int. J. Nanomed. 14, 9217–9234.
John, A., Reddy, P.H., 2021. Synaptic basis of Alzheimer's disease: focus on synaptic amyloid beta, P-tau and mitochondria. Ageing Res. Rev. 65, 101208.
Kaur, A., Nigam, K., Bhatnagar, I., Sukhpal, H., Awasthy, S., Shankar, S., Tyagi, A., Dang, S., 2020. Treatment of Alzheimer's diseases using donepezil nanoemulsion: an intranasal approach. Drug Deliv Transl Res 10, 1862–1875.
Kaushal, S., Nanda, S.S., Samal, S., Yi, D.K., 2020. Strategies for the development of metallic-nanoparticle-based label-free biosensors and their biomedical applications. Chembiochem 21, 576–600.
Kaushik, A., Jayant, R.D., Tiwari, S., Vashist, A., Nair, M., 2016. Nano-biosensors to detect beta-amyloid for Alzheimer's disease management. Biosens. Bioelectron. 80, 273–287.
Kong, L., Li, X.T., Ni, Y.N., Xiao, H.H., Yao, Y.J., Wang, Y.Y., Ju, R.J., Li, H.Y., Liu, J.J., Fu, M., Wu, Y.T., Yang, J.X., Cheng, L., 2020. Transferrin-modified osthole PEGylated liposomes travel the blood-brain barrier and mitigate Alzheimer's disease-related pathology in APP/PS-1 mice. Int. J. Nanomed. 15, 2841–2858.
Kumar, J., Meena, P., Singh, A., Jameel, E., Maqbool, M., Mobashir, M., Shandilya, A., Tiwari, M., Hoda, N., Jayaram, B., 2016. Synthesis and screening of triazolopyrimidine scaffold as multi-functional agents for Alzheimer's disease therapies. Eur. J. Med. Chem. 119, 260–277.
Laurent, C., Buée, L., Blum, D., 2018. Tau and neuroinflammation: what impact for Alzheimer's disease and tauopathies? Biomed. J. 41, 21–33.
Li, G.N., Hoffman-Kim, D., 2008. Tissue-engineered platforms of axon guidance. Tissue Eng. B Rev. 14, 33–51.
Li, J., Feng, Z., Gu, N., Yang, F., 2020. Superparamagnetic iron oxide nanoparticles assembled magnetic nanobubbles and their application for neural stem cells labeling. J. Mater. Sci. Technol. 63, 124–132.
Li, W., Luo, R., Lin, X., Jadhav, A.D., Zhang, Z., Yan, L., Chan, C.Y., Chen, X., He, J., Chen, C.H., Shi, P., 2015. Remote modulation of neural activities via near-infrared triggered release of biomolecules. Biomaterials 65, 76–85.
Lim, J.Y.C., Lin, Q., Xue, K., Loh, X.J., 2019. Recent advances in supramolecular hydrogels for biomedical applications. Materials Today Advances 3, 100021.
Liu, P.-P., Xie, Y., Meng, X.-Y., Kang, J.-S., 2019. History and progress of hypotheses and clinical trials for Alzheimer's disease. Signal Transduction and Targeted Therapy 4, 29.
Liu, X., Holzwarth, J.M., Ma, P.X., 2012. Functionalized synthetic biodegradable polymer scaffolds for tissue engineering. Macromol. Biosci. 12, 911–919.
Liu, X.G., Zhang, L., Lu, S., Liu, D.Q., Zhang, L.X., Yu, X.L., Liu, R.T., 2020. Multifunctional superparamagnetic iron oxide nanoparticles conjugated with Aβ oligomer-specific scFv antibody and class A scavenger receptor activator show early diagnostic potentials for Alzheimer's disease. Int. J. Nanomed. 15, 4919–4932.
Lopez-Barbosa, N., Garcia, J.G., Cifuentes, J., Castro, L.M., Vargas, F., Ostos, C., Cardona-Gomez, G.P., Hernandez, A.M., Cruz, J.C., 2020. Multifunctional magnetite nanoparticles to enable delivery of siRNA for the potential treatment of Alzheimer's. Drug Deliv. 27, 864–875.
Lu, N.H., How, S.C., Lin, C.Y., Tsai, S.L., Bednarikova, Z., Fedunova, D., Gazova, Z., Wu, J.W., Wang, S.S., 2018. Examining the effects of dextran-based polymer-coated nanoparticles on amyloid fibrillogenesis of human insulin. Colloids Surf. B Biointerfaces 172, 674–683.
Lu, Y., Guo, Z., Zhang, Y., Li, C., Zhang, Y., Guo, Q., Chen, Q., Chen, X., He, X., Liu, L., Ruan, C., Sun, T., Ji, B., Lu, W., Jiang, C., 2019. Microenvironment remodeling micelles for Alzheimer's disease therapy by early modulation of activated microglia. Adv. Sci. 6, 1801586.
Majidi, S., Sehrig, F.Z., Farkhani, S.M., Goloujeh, M.S., Akbarzadeh, A., 2016. Current methods for synthesis of magnetic nanoparticles. Artif Cells Nanomed Biotechnol 44, 722–734.
Manivasagan, P., Quang Bui, N., Bharathiraja, S., Santha Moorthy, M., Oh, Y.O., Song, K., Seo, H., Yoon, M., Oh, J., 2017. Multifunctional biocompatible chitosan-polypyrrole nanocomposites as novel agents for photoacoustic imaging-guided photothermal ablation of cancer. Sci. Rep. 7, 43593.
Mars, A., Hamami, M., Bechnak, L., Patra, D., Raouafi, N., 2018. Curcumin-graphene quantum dots for dual mode sensing platform: electrochemical and fluorescence detection of APOe4, responsible of Alzheimer's disease. Anal. Chim. Acta 1036, 141–146.
Martino, N., Feyen, P., Porro, M., Bossio, C., Zucchetti, E., Ghezzi, D., Benfenati, F., Lanzani, G., Antognazza, M.R., 2015. Photothermal cellular stimulation in functional bio-polymer interfaces. Sci. Rep. 5, 8911.
Matilainen, O., Quirós, P.M., Auwerx, J., 2017. Mitochondria and epigenetics - crosstalk in homeostasis and stress. Trends Cell Biol. 27, 453–463.
Md, S., Gan, S.Y., Haw, Y.H., Ho, C.L., Wong, S., Choudhury, H., 2018. In vitro neuroprotective effects of naringenin nanoemulsion against β-amyloid toxicity through the regulation of amyloidogenesis and tau phosphorylation. Int. J. Biol. Macromol. 118, 1211–1219.
Medina-Sánchez, M., Miserere, S., Morales-Narváez, E., Merkoçi, A., 2014. On-chip magneto-immunoassay for Alzheimer's biomarker electrochemical detection by using quantum dots as labels. Biosens. Bioelectron. 54, 279–284.
Mendes, I.T., Ruela, A.L.M., Carvalho, F.C., Freitas, J.T.J., Bonfilio, R., Pereira, G.R., 2019. Development and characterization of nanostructured lipid carrier-based gels for the transdermal delivery of donepezil. Colloids Surf. B Biointerfaces 177, 274–281.
Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B., Cesari, M., Nourhashemi, F., 2013. Proinflammatory cytokines, aging, and age-related diseases. J. Am. Med. Dir. Assoc. 14, 877–882.
Ni, Y.N., Kong, L., Li, X.T., Xiao, H.H., Wu, Y.T., Liang, X.C., Lin, Y., Li, W.Y., Deng, Y., Li, Y., Shi, Y., Cheng, L., Li, H.Y., Ju, R.J., Yang, J.X., 2020. Multifunctional osthole liposomes and brain targeting functionality with potential applications in a mouse model of Alzheimer's disease. J. Liposome Res. 1–12.
Nikolova, M.P., Chavali, M.S., 2019. Recent advances in biomaterials for 3D scaffolds: a review. Bioact Mater 4, 271–292.
Niwa, K., Younkin, L., Ebeling, C., Turner, S.K., Westaway, D., Younkin, S., Ashe, K.H., Carlson, G.A., Iadecola, C., 2000. Abeta 1-40-related reduction in functional hyperemia in mouse neocortex during somatosensory activation. Proc. Natl. Acad. Sci. U. S. A. 97, 9735–9740.
Orive, G., Anitua, E., Pedraz, J.L., Emerich, D.F., 2009. Biomaterials for promoting brain protection, repair and regeneration. Nat. Rev. Neurosci. 10, 682–692.
Pinheiro, R.G.R., Granja, A., Loureiro, J.A., Pereira, M.C., Pinheiro, M., Neves, A.R., Reis, S., 2020. Quercetin lipid nanoparticles functionalized with transferrin for Alzheimer's disease. Eur. J. Pharmaceut. Sci. 148, 105314.
Pluvinage, J.V., Haney, M.S., Smith, B.A.H., Sun, J., Iram, T., Bonanno, L., Li, L., Lee, D. P., Morgens, D.W., Yang, A.C., Shuken, S.R., Gate, D., Scott, M., Khatri, P., Luo, J., Bertozzi, C.R., Bassik, M.C., Wyss-Coray, T., 2019. CD22 blockade restores homeostatic microglial phagocytosis in ageing brains. Nature 568, 187–192.
Rajput, A., Bariya, A., Allam, A., Othman, S., Butani, S.B., 2018. In situ nanostructured hydrogel of resveratrol for brain targeting: in vitro-in vivo characterization. Drug Deliv Transl Res 8, 1460–1470.
Rao, N.V., Ko, H., Lee, J., Park, J.H., 2018. Recent progress and advances in stimuli-responsive polymers for cancer therapy. Front Bioeng Biotechnol 6, 110.
Razzino, C.A., Serafín, V., Gamella, M., Pedrero, M., Montero-Calle, A., Barderas, R., Calero, M., Lobo, A.O., Yáñez-Sedeño, P., Campuzano, S., Pingarrón, J.M., 2020. An electrochemical immunosensor using gold nanoparticles-PAMAM-nanostructured screen-printed carbon electrodes for tau protein determination in plasma and brain tissues from Alzheimer patients. Biosens. Bioelectron. 163, 112238.
Ruitenberg, A., den Heijer, T., Bakker, S.L., van Swieten, J.C., Koudstaal, P.J., Hofman, A., Breteler, M.M., 2005. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. Ann. Neurol. 57, 789–794.
Ruther, R.E., Cui, Q., Hamers, R.J., 2013. Conformational disorder enhances electron transfer through alkyl monolayers: ferrocene on conductive diamond. J. Am. Chem. Soc. 135, 5751–5761.
Saffari, P.M., Alijanpour, S., Takzaree, N., Sahebgharani, M., Etemad-Moghadam, S., Noorbakhsh, F., Partoazar, A., 2020. Metformin loaded phosphatidylserine nanoliposomes improve memory deficit and reduce neuroinflammation in streptozotocin-induced Alzheimer's disease model. Life Sci. 255, 117861.
Sanati, M., Khodagholi, F., Aminyavari, S., Ghasemi, F., Gholami, M., Kebriaeezadeh, A., Sabzevari, O., Hajipour, M.J., Imani, M., Mahmoudi, M., Sharifzadeh, M., 2019. Impact of gold nanoparticles on amyloid β-induced Alzheimer's disease in a rat animal model: involvement of STIM proteins. ACS Chem. Neurosci. 10, 2299–2309.
Sathya, S., Shanmuganathan, B., Devi, K.P., 2020. Deciphering the anti-apoptotic potential of α-bisabolol loaded solid lipid nanoparticles against Aβ induced neurotoxicity in Neuro-2a cells. Colloids Surf. B Biointerfaces 190, 110948.
Sathya, S., Shanmuganathan, B., Manirathinam, G., Ruckmani, K., Devi, K.P., 2018. α-Bisabolol loaded solid lipid nanoparticles attenuates Aβ aggregation and protects Neuro-2a cells from Aβ induced neurotoxicity. J. Mol. Liq. 264, 431–441.
Shah, S., Leon, L., 2021. Structural dynamics, phase behavior, and applications of polyelectrolyte complex micelles. Curr. Opin. Colloid Interface Sci., 101424
Shan, D., Ma, C., Yang, J., 2019. Enabling biodegradable functional biomaterials for the management of neurological disorders. Adv. Drug Deliv. Rev. 148, 219–238.
Simpson, L.W., Szeto, G.L., Boukari, H., Good, T.A., Leach, J.B., 2020. Collagen hydrogel confinement of Amyloid-β (Aβ) accelerates aggregation and reduces cytotoxic effects. Acta Biomater. 112, 164–173.
Smith, C.D., Andersen, A.H., Kryscio, R.J., Schmitt, F.A., Kindy, M.S., Blonder, L.X., Avison, M.J., 1999. Altered brain activation in cognitively intact individuals at high risk for Alzheimer's disease. Neurology 53, 1391–1396.

Song, R., Murphy, M., Li, C., Ting, K., Soo, C., Zheng, Z., 2018. Current development of biodegradable polymeric materials for biomedical applications. Drug Des. Dev. Ther. 12, 3117–3145.
Sung, Y.K., Kim, S.W., 2020. Recent advances in polymeric drug delivery systems. Biomater. Res. 24, 12.
Tang, M., Pi, J., Long, Y., Huang, N., Cheng, Y., Zheng, H., 2018. Quantum dots-based sandwich immunoassay for sensitive detection of Alzheimer's disease-related Aβ1–42. Spectrochim. Acta Mol. Biomol. Spectrosc. 201, 82–87.
Thanh, N.T.K., Green, L.A.W., 2010. Functionalisation of nanoparticles for biomedical applications. Nano Today 5, 213–230.
Thomas, L., Zakir, F., Mirza, M.A., Anwer, M.K., Ahmad, F.J., Iqbal, Z., 2017. Development of Curcumin loaded chitosan polymer based nanoemulsion gel: in vitro, ex vivo evaluation and in vivo wound healing studies. Int. J. Biol. Macromol. 101, 569–579.
Tian, B., Hua, S., Tian, Y., Liu, J., 2020. Chemical and physical chitosan hydrogels as prospective carriers for drug delivery: a review. J. Mater. Chem. B 8, 10050–10064.
Venkatramani, A., Panda, D., 2019. Regulation of neuronal microtubule dynamics by tau: implications for tauopathies. Int. J. Biol. Macromol. 133, 473–483.
Wahsner, J., Gale, E.M., Rodríguez-Rodríguez, A., Caravan, P., 2019. Chemistry of MRI contrast agents: current challenges and new frontiers. Chem. Rev. 119, 957–1057.
Wells, C.M., Harris, M., Choi, L., Murali, V.P., Guerra, F.D., Jennings, J.A., 2019. Stimuli-responsive drug release from smart polymers. J. Funct. Biomater. 10.
Wu, Y., Wang, L., Guo, B., Shao, Y., Ma, P.X., 2016. Electroactive biodegradable polyurethane significantly enhanced Schwann cells myelin gene expression and neurotrophin secretion for peripheral nerve tissue engineering. Biomaterials 87, 18–31.
Xiao, S., Zhou, D., Luan, P., Gu, B., Feng, L., Fan, S., Liao, W., Fang, W., Yang, L., Tao, E., Guo, R., Liu, J., 2016. Graphene quantum dots conjugated neuroprotective peptide improve learning and memory capability. Biomaterials 106, 98–110.
Xu, H., Holzwarth, J.M., Yan, Y., Xu, P., Zheng, H., Yin, Y., Li, S., Ma, P.X., 2014. Conductive PPY/PDLLA conduit for peripheral nerve regeneration. Biomaterials 35, 225–235.
Yadav, A., Sunkaria, A., Singhal, N., Sandhir, R., 2018. Resveratrol loaded solid lipid nanoparticles attenuate mitochondrial oxidative stress in vascular dementia by activating Nrf2/HO-1 pathway. Neurochem. Int. 112, 239–254.
Yang, P., Sheng, D., Guo, Q., Wang, P., Xu, S., Qian, K., Li, Y., Cheng, Y., Wang, L., Lu, W., Zhang, Q., 2020. Neuronal mitochondria-targeted micelles relieving oxidative stress for delayed progression of Alzheimer's disease. Biomaterials 238, 119844.
Yuan, Q., Wang, T., Yu, P., Zhang, H., Zhang, H., Ji, W., 2021. A review on the electroluminescence properties of quantum-dot light-emitting diodes. Org. Electron. 90, 106086.
Zameer, S., Ali, J., Vohora, D., Najmi, A.K., Akhtar, M., 2020. Development, optimisation and evaluation of chitosan nanoparticles of alendronate against Alzheimer's disease in intracerebroventricular streptozotocin model for brain delivery. J. Drug Target. 1–18.
Zhou, H., Gong, Y., Liu, Y., Huang, A., Zhu, X., Liu, J., Yuan, G., Zhang, L., Wei, J.A., Liu, J., 2020. Intelligently thermoresponsive flower-like hollow nano-ruthenium system for sustained release of nerve growth factor to inhibit hyperphosphorylation of tau and neuronal damage for the treatment of Alzheimer's disease. Biomaterials 237, 119822.
Zhou, J., Fa, H., Yin, W., Zhang, J., Hou, C., Huo, D., Zhang, D., Zhang, H., 2014. Synthesis of superparamagnetic iron oxide nanoparticles coated with a DDNP-carboxyl derivative for in vitro magnetic resonance imaging of Alzheimer's disease. Mater. Sci. Eng. C 37, 348–355.