Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2023, Vol. 39, No.(2):
Pg. 263-275

Nano Based Approach for the Neurological Disorder Treatments-A Scenario (A-Review)

AJAY KUMAR OLI[1]*, APOORVA JAIN[1], NAGAVENI SHIVSHETTY[2], PALAKSHA KANIVE JAVAREGOWDA[1] and KELMANI CHANDRAKANTH.R[3]

[1]Department of Biomedical Science, SDM Research Institute for Biomedical Sciences Shri Dharmasthala Manjunatheshwara University, 5th Floor, Manjushree Building, SDM College of Medical Sciences and Hospital Campus, Sattur, Dharwad, Karnataka, 580009, India.
[2]Department of Microbiology/ Food Science and Technology, GITAM Institute of Science, GITAM (Deemed to be University), Gandhi Nagar, Rushikonda, Visakhapatnam, 530045, Andhra Pradesh, India.
[3]Department of Biotechnology, Jnana Ganga Campus, Gulbarga University, Kalaburagi, 585106, Karnataka, India.
*Corresponding author E-mail: ajay.moli@gmail.com

http://dx.doi.org/10.13005/ojc/390205

(Received: January 03, 2023; Accepted: April 04, 2023)

ABSTRACT

The prevalence of neurological illnesses is a leading cause of mortality and disability is rising globally. It is the second greatest cause of death globally. Multiple years of life adjusted for incidence of death and disability (DALY), the sum of years of life lost (YLLs) and years lived with disability (YLDs) by age and sex, are used to classify 15 neurological illnesses. Alzheimer's, Parkinson's, a stroke, Huntington's disease, and epilepsy are a few of them. Therefore, it is crucial to design and create novel delivery systems that could transport the therapeutic medications or diagnostic tools needed to treat neurological illnesses. In this overview, we go through fresh methods for improving medication absorption by the central nervous system (CNS). The treatment of neurological diseases, particularly those with neurodegenerative features, has a significant deal of potential to be impacted by nanotechnology. According to a number of studies, neurodegenerative CNS illnesses have been successfully treated with nanomaterials. The most effective usage of nanomaterials is the treatment of CNS disorders, which improves the overall impact of the medication and highlights the significance of nanotherapeutics.

Keywords: Central Nervous system, Liposomes, Neurological disorder, Nanoparticles, Stroke.

INTRODUCTION

The nervous system is a multifaceted system that controls numerous bodily processes and actions, including regulation and synchronization. The central nervous system (CNS) and peripheral nervous system (PNS) are two basic parts. The brain and spinal cord are parts of the CNS, which is known as the "central processing station." All other neural components are a part of the PNS,

which also conveys sensory data from the muscles, tissues, and nerves in the rest of the body to the brain[1]. The phrase "neurological disorder" describes a condition affecting the central nervous system (CNS), including physical harm to the brain, spinal cord, or nerves that influence the CNS. Another result that could point to the disease's etiology is a change in specific biochemical properties or another, unidentified factor that has an impact on the CNS.

Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and several other disorders are types of neurological disorders that affect the brain and its functions. In cerebrovascular diseases, the main diseases are stroke or migraine and headache. neurological disorders are affected by nerve-infecting agents such as viruses, bacteria, and fungi. Psychiatric disorders are conditions that affect the brain, nervous system, or both. (Fig.1) They can be caused by physical or chemical factors that can cause abnormal behavior or feeling and are caused by stress[2].

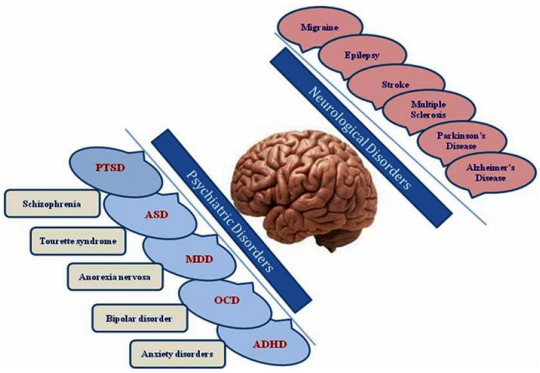

Fig. 1. Represents types of Neurological and Psychiatric disorders

Nanomaterials for diagnosis, monitoring, and control are another word for nanotechnology utilized in medicine. Disease prevention and treatment are frequently referred to as nanotechnology[3]. Nanotechnology has become a part of our daily life over time. An integrated strategy is being used to apply this pertinent technology in various contexts. Nanomaterials are now being used in the creation of new treatments, or at the very least, promises based on nanotechnology are being made. The use of nanotechnology in new medications is now being studied, and in the EU, it has gained recognition as a significant technology that can offer novel answers to unmet medical needs[4-6].

Nanoparticles (NPs), a product of nanotechnology, have been utilized in medicine to identify, treat, and/or prevent human diseases. the sizes of nanoparticles, such as biomolecules like proteins (1-20nm), DNA (diameter of 2nm), hemoglobin (5nm), viruses (20nm), and cell membranes (6-10nm). It has been suggested that the range of nanoscale materials and technologies in nanomedicine be increased to 1000nm.[7-8]

Nanomaterials can enter the body in a variety of ways, such as through the airways, skin, gastrointestinal tract, and medication injections, where they are then transported to the organs where they work biologically (such as oxidative stress, cellular apoptosis, inflammatory responses, and DNA damage). Because they can load and transport an incredibly diverse range of medications to practically any organ or region of the body, NPs have been a hot topic in drug delivery research. This results in focused, regulated, and long-lasting therapeutic effects9. Drugs or other bioactive compounds have been dissolved, encapsulated, and bound in nanoparticles by researchers. Studies have shown that this method can be used to transport both hydrophilic and hydrophobic drugs, biological macromolecules, proteins, and even vaccines. In comparison to microparticles, nanoparticles have a number of advantages, like their suitability for intravenous delivery, their enormous potential for the controlled release of drugs, and their capacity to target specific sites with drugs[10-11].

Classification of nanoparticles used in the treatment of Neurological Disorders

Nanoscale engineering used in a range of sectors is referred to as nanotechnology. It has made it possible for researchers to create noninvasive methods for delivering imaging and therapeutic substances through brain barriers[12–13]. Consequently, the fusion of nanotechnology and neurology has given rise to a brand-new industry called neuro nanomedicine. Researchers are able to identify and cure problems of the central nervous system using this technique, which makes use of nanomaterials, nanoformulations, and nanofabrication procedures.

The following nanoparticles have been utilized to deliver therapeutic as well as imaging agents to the brain such as dendrimers, micelles, liposomes, quantum

dots, viral vectors, carbon nanotubes, and extracellular vesicles. The interest in these nanoparticles has increased during the past ten years[14-15].

Polymeric Nanoparticles

Matrix architectures are mostly seen in the form of nanospheres and nanocapsules. They are polymeric nanoparticles that are utilized as non-carriers. The biocompatible and biodegradable polymers that are most frequently used to create these nanocarriers are polylactic acid, polylactide-co-polyglycolic acid, polyglycolic acid, poly (-caprolactone), polymethyl methacrylate, as well as natural polymers like chitosan, alginate, gelatin, and albumin[16-19] Figure 2.

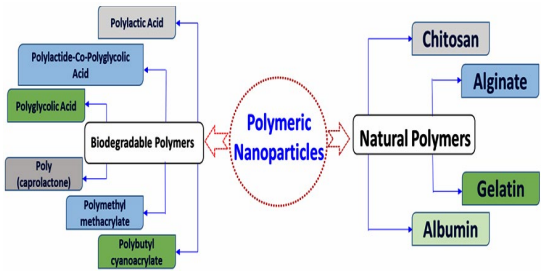

Fig. 2. Different types of Polymeric nanoparticles used in the treatment of Neurological disorders

Reports on improved medication supply to the brain are facilitated by polymeric polymer NPs available. Mice were given NPs from PLGA carrying anti-tuberculosis medications (isoniazid, pyrazinamide, rifampicin, and ethambutol), which maintained high drug levels for 5-8 days in plasma and 9 days in the brain, significantly longer than in comparison with free medications. Functional proteins have been delivered successfully into neurons and neuronal cell lines using polybutylcyanoacrylate (PBCA) nanoparticles[20]. Polybutylcyanoacrylate (PBCA) NPs have been used successfully to deliver functional proteins into neurons and neuronal cell lines[21-22].

It has been extensively studied how the brain absorbs and releases drugs from polymeric nanoparticles to develop nanocarriers that could efficiently transport medications to the central nervous system through systemic and also local delivery. Therefore, the primary possibilities are endocytosis or transcytosis using endothelial cells. High concentration gradient accumulation in brain capillaries that transfers to the brain parenchyma, lipid solubilization by membrane fluidization due to surfactant action, the opening of tight junctions, etc., and restricted efflux phenomena by coating polymers with polysorbates are a few examples. The surface of the polymeric nanoparticles can also be functionalized by conjugating certain peptides or cell-penetrating ligands to improve transcytosis across the BBB[23-24].

Solid Lipid Nanoparticles

The medicine can be dissolved or disseminated inside solid lipid nanoparticles (SLN), which are lipid-based nanocarriers that are stable and have a solid hydrophobic lipid core. They are created using lipids that are biocompatible, such as waxes, fatty acids, or triglycerides. They are typically tiny (40–200nm), which enables them to pass through the reticuloendothelial system (RES) and narrow BBB endothelial cells[25-26]. These solid lipids stearic acid, cetyl alcohol, carnauba wax, beeswax, cholesterol, butyrate, and emulsifying wax are the most frequently used when creating these nanocarriers[27-28] Figure 3.

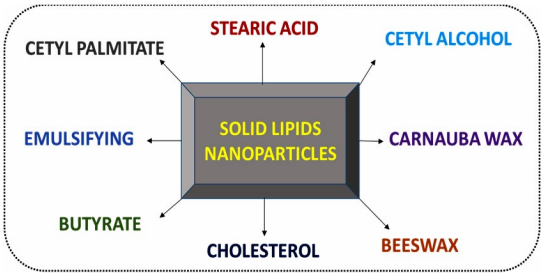

Fig. 3. Types of Solid Lipids Nanoparticles used in the treatment of Neurological disorders

We created a substance called 3,5-dioctaoyl-5-fluoro-2-deoxyuridine to overcome the medicine 5-fluro-2-dexoyuridine's (FUdR) poor accessibility and its inclusion into solid lipid nanoparticles as a delivery mechanism (DO-FUdR). According to the findings, free FUdR had a roughly 2-fold worse in vivo brain targeting efficacy than DO-FUdR-SLN. For the treatment of illnesses of the central nervous system like Alzheimer's disease, SLN is a promising drug delivery system that can increase the ability of medications to enter through the BBB[29-30].

The main processes for the uptake of SLN into the brain are endocytosis, passive diffusion, active transport, and tight junctions opening in the brain microvasculature. Additionally, apolipoprotein E receptor functionalization of SLN has emerged as a key strategy for enhancing brain-directed[31-34].

Liposomes

Liposomes are man-made, spherical vesicles with an aqueous solution core surrounded by one or more amphiphilic lipid bilayers. Based on the size and the number of lamellae, liposomes are divided into three categories: small unilamellar vesicles (SUV) up to 100nm in size, a bilayer, and large unilamellar vesicle (LUV) with a size>100nm, and a bilayer and multilamellar vesicle (MLV)[35-36]. Liposomes have been produced as nanocarriers to efficiently transport therapeutic molecules such as vaccines, enzymes, drugs, nucleic acids, proteins, and imaging agents[37–38]. They are used to provide medications for cerebral ischemia, opioid peptide administration, and the treatment of brain tumours[39-41]. Liposomes mostly enter the brain parenchyma via receptor-mediated endocytosis, adsorption-mediated transcytosis, and BBB breach caused by external pressure[42].

Cationic Liposomes

Cationic liposomes, carrying positively charged lipids, were developed as transfection vehicles to deliver genetic material (e.g. DNA) into cells while avoiding lysosomal degradation. One of the most commonly used cationic lipids is 1,2-dioleoyl-3-trimethyl-ammonium propane (DOTAP), mixed with dioleoyl phosphatidylethanolamine (DOPE). Cholesterol also increases transfection levels and may reduce liposome destabilization in the presence of serum[43]. Small unilamellar vesicles (SUV) up to 100 are the classification for liposomes. The complex known as a lipoplex is created when cationic lipids and nucleic acids are combined. When pH 5-6 is reached, DOPE fuses with the endosomal membrane, destabilizes it, and releases its contents into the cytosol. Therefore, similar to DNA, drugs could be a vehicle in endothelial cells, improving their crossing barriers and reaching neurons. In a study, researchers transfected liposomes containing photoreactive drugs to glioblastoma cells and found that the liposomes were able to enhance drug delivery of paclitaxel to the brain *In-vivo* rodents[44-47].

Polymeric Micelles

Amphiphilic copolymers aggregate to produce polymeric micelles, which are spherical structures having a hydrophilic shell and a hydrophobic center. These polymeric micelles have good stability[48]. Chitosan-conjugated Pluronic nanocarriers along with a specific brain targeting peptide (rabies virus glycoprotein; RVG29) inoculated i.v. injection into mice showed accumulation in the brain *In-vivo*, these nanocarriers can either be a quantum dot fluorophore conjugated to a protein loaded into the carrier. Other study reports have shown an increased central analgesic effect of the micellar vehicle drug[49].

Amphiphilic molecules' ability to self-assemble is a key component of the mechanisms that produce micelles. Their structure is defined by an inner core made up of the hydrophobic/non-polar tail section of the molecule and an outside surface that covers the head part of the molecule. By offering chemical and physical stability, continuous release, and control over the release, micelles have the potential to boost medicine bioavailability and deliver poorly water-soluble and lipophilic compounds. Micelles mostly cross the BBB using the endocytosis and/or transcytosis pathways. Additionally, the BBB can be damaged by applying external heat or mechanical stresses, conjugating certain ligands and antibodies, or increasing the penetrating capacity[50-51].

Dendrimers

Dendrimers are branched polymers that resemble a tree. A dendrimer normally has symmetry at its core, but when it is sufficiently expanded, it frequently takes on a three-dimensional spheroidal shape in the water. A central core consists of at least two identical chemical functional groups, followed by repeating units of other molecules. Other molecules develop at least one branching junction thanks to their branching junctions. Chains and branches are repeated, resulting in a sequence of crowded, concentric layers. Therefore, the structure is tightly packed in the periphery, leaving spaces that have a key role in the drug-trapping ability of dendrimers[52]. The most widely used dendrimer molecules are polyamidonamine, polypropylenimine, and polyaryl ethers[53]. Following interparenchymal or interventricular injections, poly(amidoamine), or PAMAM dendrimers, demonstrated a striking capacity for diffusing in the CNS tissue *In-vivo* and penetrating living neurons. In another study PAMAM is systemically administered localized in activated microglia and astrocytes in the brain of newborn rabbits with cerebral palsy, providing clinical translation possibility in the treatment of neuro-inflammatory disorders in humans[54]. Since dendrimers can pass the BBB, they are

frequently used in the treatment of illnesses of the central nervous system. Through the process of cellular internalization, which is mediated by endocytosis, they can also pass through different cell membranes or biological barriers. Cellular absorption is mediated primarily by the reversible regulation of tight junction proteins such as occludin and actin. Additionally, particular ligands can be coupled to the dendrimer surfaces for improved brain targeting and easier BBB trafficking[55-56].

Inorganic nanoparticles

Inorganic nanoparticles have physicochemical properties undersized and surface plasmon behavior; it is widely used to treat treatment neurological disorders. The best examples are magnetic nanoparticles (iron oxide), platinum, chromium, manganese, gold, zinc, titanium molybdenum, and selenium. Bimetallic nanoshells and nanocages have been continuously used to enable their use as a therapeutic and diagnostic agent[57].

Gold nanoparticles

Gold nanoparticles have many desired properties, including stability, oxidation resistance, and biocompatibility. Systems for the distribution of drugs can be made using AuNPs. AuNPs with a diameter of less than 50nm have been shown to permeate the BBB. In order to treat addiction, critical proteins (DARPP-32), extracellular signal-regulated kinase (ERK), and protein phosphate I (PP-1) expression have been targeted and reduced via gold nanorod-DARPP-32 siRNA complexes (nanoplexes)[58].

Magnetic nanoparticles

These magnetic nanoparticles have a wide range of additional biomedical applications due to their high field irreversibility, high saturation field, superparamagnetism, and extra anisotropy. Application of external stimuli, such as magnetic field and near-infrared light, could promote drug release on demand across the BBB and enhance tissue imaging to maximize brain uptake of these nanoparticles. Additionally, inorganic nanoparticles are a strong possibility for brain cancer treatment because of their long-lasting increased permeability and retention effect[59].

Carbon nanotubes (CNTs)

Because of their inherent mechanical, electrical, and physico-chemical properties, CNTs are the type of nanomaterial that has generated the most scientific interest[60]. Due to the exceptional physical characteristics of these nanomaterials and their recently discovered capacity to interface with neural circuits, synapses, and membranes, CNT-based technologies are predicted to be very helpful in aiding the functional recovery of neurons after brain trauma[61]. Neutrophins are proteins that were first identified as having an impact on the survival of sensory and sympathetic neurons. CNTs can be used to distribute neutrophins, which are crucial for the growth and operation of neurons in both the CNS and PNS[62].

Quantum Dots

Quantum dots are nanomaterials of zero-dimensional with exceptional optical and electrical properties which are widely used in the scientific field. The small hydrodynamic size (10-20nm) of functionalized QDs is been reported to resemble the labeling of neurons and glial cells and tracking. QD applications in the brain have been applied in both fundamental research and clinical investigation, correlating with the interest in using functionalized QDs as drug delivery vehicles or targeted-imaging biomarkers for treating diseases of the central nervous system (CNS)[63].

Application of Nanotechnology in Neurological Disorders

Alzheimer's disease (AD)

Alzheimer's disease (AD) is characterized by a deteriorating memory, unstable emotions, and cognitive impairment that are connected to the degeneration and death of neurons in the limbic areas (hippocampus, amygdale, and their associated cortices). Basically, there are two key neuropathological indicators of AD: extracellular senile plaques produced by amyloid-(A) peptide aggregation and intracellular neurofibrillary tangles made of filaments of hyperphosphorylated Tau protein[64]. For the benefit of AD patients, a wide variety of nano-formulations have been created. PEG-stabilized nanomicelles made of phospholipids were found to reduce the neurotoxicity caused by A and prevent its aggregation in the SHY-HY human neuroblastoma cell line *In vitro*[65]. Curcumin's bioavailability was improved by its nanoliposomal formulation without affecting its capacity to prevent A aggregation. It is effective for copper chelator-loaded microemulsion nanoparticles

to penetrate the BBB and dissolve the pre-existing A aggregates *In vitro*[66-67].

Lack of the neurotransmitter acetylcholine (Ach) is another pathologic hallmark of AD. Direct infusion of free Ach is ineffective for correcting the imbalance in Ach due to its quicker breakdown in blood. When kainic acid is produced in a mouse model, the nanotechnology technique has demonstrated that Ach loaded in carbon nanotubes can restore considerable cognitive abilities to pre-AD levels as compared to free Ach[68].

Parkinson's disease

Muscle rigidity, resting tremor, postural instability, and slowed physical movement are all indications of Parkinson's disease (PD), a prevalent neurological condition (bradykinesia). Lewy bodies are clusters of alpha-synuclei found in the brain's substantia nigra, a part known for its production of dopamine. This condition is marked by the progressive loss of dopaminergic neurons and an increase in fibrillar α-synuclei. Degenerative motor symptoms in Parkinson's disease (PD) are thought to be caused by the loss of dopaminergic neurons in the SNC, which results in dopamine (DA) depletion[69-70].

Antisense oligonucleotides and PEG and polyethyleneimine nanogel complexes showed effective BBB crossing *In vitro*. Additionally, when administered intravenously, the oligonucleotides were more effectively transported to the brain, especially when the gels were functionalized with Tf or insulin molecules[71]. Researchers Zhang *et al.,* found that a single intravenous injection of plasmids encoding tyrosine hydroxylase and Tf receptor antibody coupled PEGylated liposomes corrected motor impairments in rats using the 6-hydroxydopamine (6-OHDA) model of Parkinson's disease[72]. The basic symptoms of PD are relieved by nerve growth factor (NGF) bound to PBCA nanoparticles and L-Dopa encapsulated nanoparticles that pass the blood-brain barrier. Schisantherin A (SA) nanoparticles are effective in treating PC in a model using zebrafish larvae. SA encapsulated nanoparticles formulation that boosted brain absorption and prolonged SA circulation in the bloodstream also demonstrated neuroprotective benefits in zebrafish and a cell culture model for Parkinson's disease[73-74].

Stroke

The blood supply to the brain is cut off during a stroke, depriving the tissue of oxygen and nutrients and ultimately resulting in cell and tissue death. Strokes are one of the most prevalent causes of human impairment and death. Ischemic and hemorrhagic strokes are the two different forms. 87% of all stroke cases are ischemic strokes, which are more frequent. Ischemic tissue can be identified by its necrotic core and variable-sized ischemic penumbra. This is because neurons in peripheral regions, known as the ischemic penumbra, may be recoverable due to residual perfusion from collateral blood arteries, whereas cell death occurs in the ischemic area in minutes due to a shortage of ATP, ionic disturbance, and other abnormalities[75-76].

Cerium oxide nanoparticles were non-toxic to neuronal (HT22) and macrophage (RAW164) cell lines and had antioxidant capabilities that support cell survival and decreased the formation of free radicals. When loaded into liposomes and given for up to 5 h after the commencement of a stroke, the small molecule Xeon gas, which has good neuroprotective qualities and has an optimal dosage range of 7–14 mg/kg, was found to reduce size in a rat model[77-78].

Huntington Disease

The link between cerium oxide nanoparticles and Huntington's disease has been established. is a condition that gradually affects one's motor, cognitive, and mental abilities and is brought on by a selective loss of neurons in the striatum and other parts of the brain. Due to a monogenic mutation in the huntingtin gene's exon 1 that causes polyglutamine (poly Q) development, the huntingtin protein (HTT) in the brain misfolds and aggregates[79]. The exact etiological mechanism of HD is yet unknown.

When rats with HD were treated with 3-nitroproponic acid using a solid lipid nanoparticle (C-SLN) encapsulated with curcumin, it was discovered that the activity of the striatum complex II had decreased. In previous research, the use of solid lipid nanoparticles (SLNs) as a reliable method of drug delivery to increase rosmarinic acid's (RA) ability to target the brain through intranasal administration has been demonstrated[80-81]. A technique for HD therapy is to target suppression of Huntington protein aggregation, although the effectiveness is subpar.

According to studies, people with HD disease have insufficient selenium (Se) levels in their brains, but improved brain selenium homeostasis may lessen neuronal loss and dysfunction. Using transgenic HD models of Caenorhabditis elegans, some research investigated the use of selenium nanoparticles (NPs) (Nano-Se) to treat HD disease by controlling HD-related neurodegeneration and cognitive loss *(C. elegans)*. At modest doses, nano-Se NPs dramatically reduced neuronal mortality, alleviated behavioral dysfunction, and shielded *C. elegans* from harm when under stress. Additionally, the molecular mechanism showed that Nano-Se reduced oxidative stress, prevented huntingtin proteins from aggregating, and reduced the expression of histone deacetylase family members at the mRNA level[82].

Tumor

Like tumours in other body regions, brain tumours can be benign, developing and existing entirely within the brain, or metastatic, developing from a tumour outside the central nervous system (CNS), the most common of which is glioblastoma multiforme (GBM), a malignant glioma. Due to their poor prognosis, difficulty in diagnosing, high rate of recurrence, and lack of readily available accessible means of delivering anti-cancer medications across BBB in an efficient concentration, they rank among the most difficult diseases to treat[83-84].

Docetaxel-incorporated albumin-lipid nanoparticles (DNPs) aggregate at the experimental glioma site in vivo and trigger apoptosis in a number of cancer cell lines *In vitro*. The EPR effect is thought to be the cause of this phenomenon. In both TMZ-resistant and TMZ-sensitive glioblastoma cells in animal models, temozolomide (TMZ)-containing liposomes with anti-transferrin receptor single-chain antibody fragments were discovered to be more efficient than free TMZ[85-86]. For the treatment of glioma, biodegradable polymer-based nanoparticles and gold nanoparticles have demonstrated potential in drug delivery across the BBB. Drug delivery to the brain using coated poly (butylcyanoacrylate) (PBCA) nanoparticles has been investigated[87-89]. In a different rat brain model study, methotrexate-transferrin conjugate-loaded polysorbate[80]-coated poly-lactic-co-glycolic acid nanoparticles were investigated and demonstrated superior tumour penetration, reduced organ toxicity, and increased anti-tumor activity when compared to non-targeting nanoparticles[90].

Epilepsy

During partial or generalized seizures, epilepsy, a CNS illness, is defined by an abnormal rise in brain electrical activity that may be localized to the focal location or diffuse across the brain[91]. The mechanisms of pharmaco-resistance in epilepsy can be explained by a number of different hypotheses. According to the neural network hypothesis, repeated episodes of excessive neuronal activity lead to structural alterations like synaptic rearrangement, neuronal degeneration, gliosis, axonal sprouting, necrosis, and neuronal axonal sprouting. These changes may aid in the development of abnormal brain networks that may result in pharmaco-resistance[92]. The blood-brain barrier (BBB), medication resistance, and recurrence of disease after drug withdrawal are just a few of the obstacles that make the existing treatment methods nearly worthless. With the least amount of toxicity to the brain and other body tissues, these methods seek to lessen seizure frequency and severity[93].

In comparison to PLGA nanoparticles coated with polysorbate-80 and SLNs loaded with carbamazepine, PLGA nanoparticles loaded with carotene had more potential for an anticonvulsant impact[94-95]. A study using liposomal muscimol formulation in rats revealed that it could reduce focal seizures with just little histological changes, and a study using amiloride-loaded liposomes in mice indicated that they had stronger anticonvulsant potential than the free medication[96-97]. According to a rat study, giving ethosuximide-loaded chitosan nanocapsules subcutaneously reduces the rise in ware discharge. Due to their ability to provide continuous drug release, these nano-formulations can be developed as depot drug delivery systems for the long-term use of antiepileptic drugs[98]. Application of the nanoparticles over the disease is as represented in figure Figure 4.

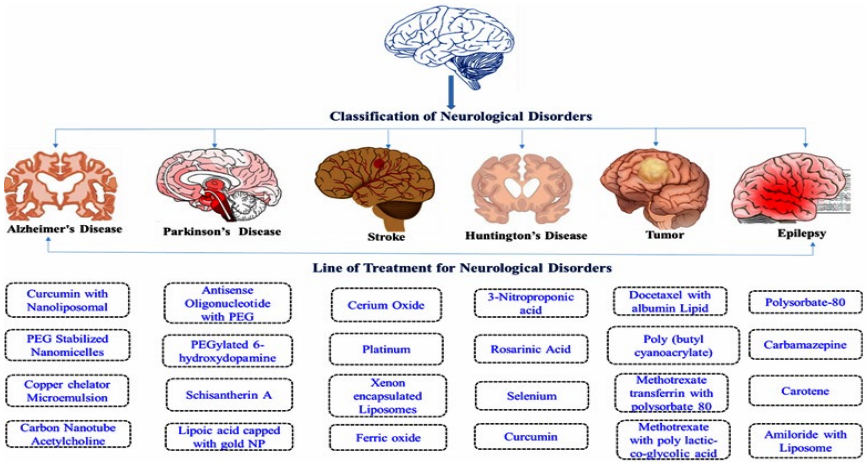

Fig. 4. Represent different nanoparticles used for the treatment of Neurological disorders

CONCLUSION

In the modern period, a collection of neurological disorders known as central nervous system (CNS) disorders have emerged as a major healthcare concern and require intense study focus to safeguard individuals against them. Numerous prospective medications have been studied to treat various neurological illnesses, but their treatment efficacy is still constrained by a number of difficulties. Nanotechnology has emerged as an interesting and promising new treatment option for neurological illnesses, and it has the ability to solve many issues with traditional therapeutic regimens. In order to deliver their payload at the pre-defined place (s) according to the given time and dose formulas, specially designed nanoparticles delivered by specially built nanocarriers could penetrate the blood-brain boundaries without being detected by the immune system. The use of nanotechnology in the delivery of CNS medications has the potential to completely change the way we approach CNS-targeted treatments, opening up new therapy options for neurological illnesses. This is because of nanoengineering of the drug/causes' ability to cross the brain-blood barrier diffuse within the brain tissue, and target specific cells or signaling systems for therapeutic delivery.

ACKNOWLEDGMENT

All the authors are thankful to Shri Dharmasthala Manjunatheshwara University, Dharwad for their valuable support.

Conflict interest

The authors have no conflict of interest to disclose.

REFERENCES

1. Simonato, M.; Bennett, J.; Boulis, N.M.; Castro, M.G.; Fink, D.J.; Goins, W.F.; Gray, S.J.; Lowenstein, P.R.; Vandenberghe, L.H.; Wilson, T.J.; Wolfe, J.H.; Glorioso, J.C., *Nature Reviews Neurology.*, **2013**, *9*, 277-291.
2. Maha, Z.R.; Ghadha, I.F.; Hanan, F.A. Neurological Disorders: causes and Treatment strategies. *International Journal of Public Mental Health and Neurosciences.*, **2018**, *5*(1), 32-40.
3. Tinkle, S.; Mcneil, S.E.; Muhlebach, S.; Bawa, R.; Borchard, G.; Barnholz, Y.C.; Tamarkin, T.; Desai, N. Nanomedicines: addressing the scientific and regulatory gap. *Ann N Y Acad Sci.*, **2014**, *1313*, 35-56.
4. Bleeker, E.A.; deJong, W.H.; Geertsma, R.E.; Groenewold, M.; Heugens, E.H.; Koers-Jacquemijins. M.; Meent D.V.; Ropma J.R.; Rietvel, A.G.; Wijnhoven W.P.S.; Cassee, R.G.; Oomen G.A. Considerations on the EU definition of a nanomaterial: science to support policy making. *Regul Toxicol Pharmacol.*, **2013**, *65*, 119-125.
5. Ossa, C.; Ma, Y.C.; Wang, Z.X. Structure-activity relationship models for hazard assessment and risk management of engineered nanomaterials. *Proc. Eng.*, **2014**, *102*, 1500-1510.

6. Pita, R.; Ehmann, F.; Papaluca, M. Nanomedicines in the EU-regulatory overview. *AAPS J*., **2016**, *18*, 1576-1582.
7. Riehemann, K.; Schneider, S.W.; Luger, T.A.; Godin, B.; Ferrari, M.; Fuchs, H. Nanomedicine challenge and perspectives. *Angew Chem Int Engl*., **2009**, *48*, 872-897.
8. Sabry, N.M.; Tolba, S.; Abdel-Gawad, F.K.; Bassem, S.M.; Nassar, H.F.; El-Taweel, G.E.; Okasha, A. Ibrahim M. Interaction between nano-silver and bacteria: Modeling approach. *Biointerface Res Chem*., **2018**, *8*, 3570-3574.
9. Hans, M.L.; Lowman, A.M. Biodegradable nanoparticles for drug delivery and targeting. *Curr Opin Solid State Mater Sci*., **2002**, *6*, 319-327.
10. Din, F.U.; Aman, W.; Ullah, I.; Qureshi, O.S.; Mustapha, O.; Shafique, S.; Zeb, A. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *Int J Nanomed*., **2017**, *12*, 7291-7309.
11. Faisal, N.; Kumar, K. Polymer and metal nanocomposites in biomedical applications. *Biointerface Res Appl Chem*., **2017**, *7*, 2286-2294.
12. Ramsden, J. J. Chapter 1-What is Nanotechnology? In Applied Nanotechnology, 3rd ed.; Ramsden JJ, Ed; William Andrew Publishing: Amsterdam, The Netherlands., **2018**, 3-13.
13. Cetin, M.; Aytekin, E.; Yavuz, B.; Bozdag-Phelivan, S. Chapter 7-Nanoscience in targeted brain drug delivery. In Nanotechnology Methods for Neurological Diseases and Brain Tumors, Gursoy-Ozdemir Y, Bodag-Phelivan S, Sekerdag E, Eds; Academic Press: Cambridge, MA, USA, **2017**, 117-147.
14. Rassolzadeh, R.; Mehrnejad, F.; Taghdir, M.; Yaghmaei, P. Theoretical investigation of interaction energies between carbon and BN nanotubes with human hepcidin peptides: Insights into the semi empirical and Monte Carlo methods. *Biointerface Res Apl Che*., **2018**, *8*, 3594-3601.
15. Feldman, D. Polymer nanocomposites for tissue engineering, antimicrobials and drug delivery. *Biointerface Res Appl Chem*., **2018**, *8,* 3153-3160.
16. Choonara, Y.E.; Pillay, V.; Ndesendo, V.M.K, Toit C.L, Kumar, P.; Khan, A.R.; Murphy, S.C.; Jarvis L.D. Polymeric emulsion and crosslink-mediated synthesis of super-stable nanoparticles as sustained-release anti-tuberculosis drug carriers. *Colloids and surface B*., **2011**, *87*(2), 243-254.
17. Pund, S.; Joshi, A. Chapter 23-Nano-architectures for neglected tropical protozoal Disease: Challenges and State of the Art. In Nano and Microscale Drug Delivery Systems; Grumezescu, A. M., Ed.; Elsevier: Amsterdam, The Netherlands., **2017**, 139-480.
18. Jevvanandam, J.; Aing, Y.S.; Chan, Y.S.; Pan, S.; Danquah, M.K. Chapter 3- Nanoformulation and Application of phytochemicals as antimicrobial agents. In Antimicrobial Nanoarchitectonics; Grumezescu, A.M., Ed; Elsevier. Amsterdam, The Netherlands., **2017**, 61-82.
19. Sengel-Truk, C.T.; Gumustas, M.; Uslu, B.; Ozkan, S.A. Chapter 10-Nanosized Drug Carriers for Oral Delivery of Anticancer compounds and the importance of the chromatographic techniques. In Nano and Microscale Drug Delivery Systems, Grumezescu, A.M. Ed.; Elsevier. Amsterdam, The Netherlands., **2017**, 165-195.
20. Yadav, S.; Sawant, K.K. Formulation optimization of etoposide loaded PLGA nanoparticles by double factorial design and their evaluation. *Curr. Drug. Deliv*., **2010**, *7*(1), 51-64.
21. Hasadri, L.; Kreuter, J.; Hattori, H.; Iwasaki, T.; George, J.M. Functional protein delivery into neurons using polymeric nanoparticles. *Journal of Biological Chemistry*., **2009**, *11* (284), 6972-6981.
22. Kabanov, A.V.; Batrakova, E.V.; Melik-Nubarov, N.S.; Fedoseev A.N.; Dorodnich Y.T.; Alakhov Y.v.; Chekhonin P.V.; Naxarova R.I.; Kabanov A.V. A new class of drug carriers: micelles of poly (oxyethylene) poly(oxypropylene) block copolymers as microcontainers for drug targeting from blood in brain. *Journal of Controlled Release*., **1992**, *2*(22), 141-157.
23. Singh, N.; Joshi, A.; Toor, A.P.; Verma, G. Chapter 27-Drug delivery: Advancements and Challenges. In Nanostructures for Drug Delivery; Andronescu, E, Grumezescu, A.M., Eds; Elsevier: Amsterdam, The Netherlands., **2017**, 865-886.

24. El-say, K.M.; El-Sawy, H.S. Polymeric nanoparticles: Promising platform for drug delivery. *Int J Pharm*., **2017**, *528*, 675-691.
25. Kaur, I.P.; Bhandari, R.; Bhandari, S.; Kakkar, V. Potential of solid lipid nanoparticles in brain targeting. *Journal of Controlled Release*., **2008**, *127*(2), 97-109.
26. Pardeshi, C.; Rajput, P.; Belgamwar, V.; Tekade, A.; Patil, G.; Chaudhary, K.; Sonje A. Solid lipid based nanocarriers: an overview. *Acta Pharmaceutica*., **2012**, *62*(4), 433-472.
27. Chifiriuc, M.C.; Kamerzan, C.; Lazar, V. Chapter 12- Essential Oils and Nanoparticles: New Strategy to Prevent Microbial Biofilms. In Nanostructures for antimicrobial therapy, Ficai, A., Grumezescu, A.M., Eds; Elsevier. Amsterdam, The Netherlands., **2017**, 279-291.
28. Joseph, M.; Trinh, H.M.; Mitra, A.K. Chapter 7- Peptide and Protein based therapeutic agents. In Emerging Nanotechnologies for Diagnostics, Drug Delivery and Medical Devices; Mitra, A, K., Cholkar K., Mandal, A., Eds; Elsevier: Boston, MA, USA., **2017**, 145-167.
29. Wang, J.X.; Sun, X.; Zhang, Z.R. Enhanced brain targeting by synthesis of 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine and incorporation into solid lipid nanoparticles. *European Journal of Pharmaceutics and Biopharmaceutics*., **2002**, *54*(3), 285-290.
30. Martins, S.; Tho, I.; Reimold, I.; Fricket, G.; Souto, E.; Ferreira, D.; Brandl, M. Brain delivery of camptothecin by means of solid lipid nanoparticles: formulation design, in vitro and *In vivo* studies. *International Journal of Pharmaceutics*., **2012**, *439*(1-2),49-62.
31. Neves, A.R.; Queiroz, J.F.; Weksler, B.; Romero, I.A.; Couraud PO, Reis S. Solid lipid nanoparticles as a vehicle for brain-targeted drug delivery: Two new strategies of functionalization with apolipoprotein E. *Nanotechnology*., **2015**, *26*, 495103.
32. Gastaldi, L.; Battaglia, L.; Piera, E.; Chirio, D.; Muntoni, E.; Solazzi, I.; Gallarate, M.; Dosio, F. Solid lipid nanoparticles as vehicles of drugs to the brain: Current state of the art. *Eur J Pharm Biopharm*., **2014**, *87*, 433-444.
33. Neves, A.R.; Queiroz, J.F.; Lima, S.A.C.; Reis, S. Apo E-Functionalization of Solid Lipid Nanoparticles enhances brain drug delivery: Uptake mechanism and transport pathways. *Bioconjugate Chem*., **2017**, *28*, 995-1004.
34. Magro, R.D.; Ornaghi, F.; Cambianica, I.; Beretta, S.; Re, F.; Muscianti, C.; Rigolio, R.; Donzelli, E.; Canta, A.; Ballarini, E.; Cavaletti, G.; Gasco, P.; Sancini G. ApoE- modified solid lipid nanoparticles: A feasible strategy to cross the blood-brain barrier. *J Control Release off J Control Release Soc*., **2017**, *249*, 103-110.
35. Daniel, M.T.; Cristina, C.; Alexandra, M.G.; Raluca, I.T. Review Neruonanomedicine: An Up-to-Date Overview. *Pharmaceutics*., **2019**, *11*, 1-23.
36. Massimo, M. Review on Nanoparticles for Brain Drug Delivery. *ISRN Biochemistry*., **2013**, 1-18.
37. Abbina, S.; Parambath, A. 14- PEGylation and its alternatives: A summary. In Engineering of Biomaterials for Drug Delivery Systems; Parambath, A, Ed.; Woodhead Publishing: Sawston, UK., **2018**, 363-376.
38. Li, S.; Johnson, J.; Peck, A, Xie Q. Near infrared fluorescent imaging of brain tumor with IR780 dye incorporated phospholipid nanoparticles. *J Transl Med*., **2017**, *15*, 15-8.
39. Ishii, T.; Asai, T.; Oyama, D.; Agato, Y.; Yasuda, N.; Fukuta, T.; Shimizu, K.; Minamino, T.; Oku, N. Treatment of cerebral ischemia-reperfusion injury with PEGlyated liposomes encapsulating FK506. *FASEB Journal*., **2013**, *27*(4), 1362-1370.
40. Lindqvist, A.; Rip, J.; Gaillard, P.J.; Bjorkman, S.; Hammarlund-Udenaes, M. Enhanced brain delivery of the opioid peptide DAMGO in glutathione PEGlyated liposomes: a micro-dialysis study. *Molecular Pharmacology*., **2013**, *10*(5), 1533-1541.
41. Orthmann, A.; Zeisig, R.; Suss, R.; Lorenz, D.; Lemm, M.; Fichtner, I. Treatment of experimental brain metastasis with MTO-liposomes: impact of fluidity and LRP-targeting on the therapeutic result. *Pharmaceutical Research*., **2012**, *29*(7), 1949-1959.
42. Zhou, Y.; Peng, Z.; Seven, E.S.; Leblanc, R. Crossing the blood- brain barrier with nanoparticles. *J Control Release*., **2018**, *270*, 290-303.
43. Jeevanandam, J.; Aing, Y.S.; Chan. Y.S.; Pan, S.; Danquah, M.K. Chapter 3- Nanoformulation and applications of phytochemicals as antimicrobial agents. In Antimicrobial Nanoarchitectonics; Grumezescu, A.M., Ed.; Elsevier: Amsterdam, The Netherlands., **2017**, 61-82.

44. Molinari, A.; Colone, M.; Calcabrini, A.; Stringaro, A.; Toccacieli, L.; Arncia, G.; Mannino, S.; Mangiola, A.; Maira, G.; Bombelli, C.; Mancini, G. Cationic liposomes, loaded with m-THPC, in photodynamic therapy for malignant glioma. *Toxicology In vitro.*, **2007**, *21*(2), 230-234.
45. Zhao, M.; Chang, J.; Fu, X.; Liang, C.; Liang, S.; Runmin, Y.; Li, A. Nano-sized cationic polymeric magnetic liposomes significantly improves drug delivery to the brain in rats. *Journal of Drug Targeting.*, **2012**, *20*(5), 416-421.
46. Kaur, I.P.; Bhandari, R.; Bhandari, S.; Kakkar, V. Potential of solid lipid nanoparticles in brain targeting. *Journal of Controlled Release.*, **2008**, *127*(2), 97-109.
47. Pardeshi, C.; Rajput, P.; Belgamwar, V.; Tekade, A.; Patil, G.; Chaudhary, K.; Sonje, A. Solid lipid based nanocarriers: an overview. *Acta Pharmaceutica.*, **2012**, *62*(4), 433-472.
48. Dutta, T.; Agashe, H.B.; Garg, M.; Balasubramanium, P.; Kabra, M.; Jain, N.K. Poly (propyleneimine) dendrimer based nanocontainers for targeting of efavirenz to human monocytes/macrophages in vitro. *Journal of Drug Targeting.*, **2007**, *15*(1), 89-98.
49. Kim, J.Y.; Choi, W.I.; Kim, Y.H.; Tae, G. Brain-targeted delivery of protein using chitosan- and RVG peptide- conjugated, pluroni-based nano-carrier. *Biomaterials.*, **2013**, *34*(4), 1170-1179.
50. Jospeh, M.; Trinh, H.M.; Mitra, A.K. Chapter-7. Peptide and protein based therapeutic agents. In Emerging Nanotechnologies for diagnostics, Drug Delivery and Medical Devices, Mitra, A, K, Cholkar, K, Mandal, A., Eds.; Elsevier. Boston, MA, USA, **2017**., 145-167.
51. Wang, X.J.; Gao, Y.P.; Lu, N.N.; Li, W.S.; Xu, J.F.; Ying, X.Y.; Wu, G.; Liao, M.H.; Tan, C.; Shao, L.X.; Lu, M.Y.; Zhang, C.; Fukunaga, K.; Han, F.; Du, Y.Z. Endogenous Polysialic Acid based micelles for calmodulin antagonist delivery against vascular dementia. *ACS Appl. Mater. Interfaces.*, **2016**, *8*, 3505-35058.
52. Albertazzi, L.; Gherardini, L.; Brondi, M.; Sato, S.S.; Bifone, A.; Pizzorusso, T.; Ratto, M.G.; Bardi, G. In vivo distribution and toxicity of PAMAM dendrimers in the central nervous system depend on their surface chemistry. *Molecular Pharmacology.,* **2013**, *10*(1), 249-260.
53. Kannan, S.; Dai, H.; Navath, R.S.; Balakrishnan, B.; Jyothi, A.; Janisse, J.; Romero, R.; Kannan, M.R. Dendrimer-based postnatal therapy for neuroinflammation and cerebral palsy in a rabbit model. *Science Translational Medicine.*, **2012**, *4*(130), 1-21.
54. Gumustas, M.; Turk, S.; Gumustas, A.; Ozkan, S.A.; Uslu, B. Chapter 5- effect of polymer based nanoparticles on the assay of antimicrobial drug delivery systems. In Multifunctional systems for combined delivery, biosensing and diagnostics; Grumezescu, A.M., Ed.; Elsevier. Amsterdam, The Netherlands., **2017**, 67-108.
55. Srinageshwar, B.; Peruzzaro, S.; Andrews, M.; Johnson, K.; Heitpas, A.; Clark, B.; Mcgurie, C.; Peterson, E.; Kippe, J.; Stewart A., Lossia, O.; Al-Gharaibeh, A.; Antcliff, A.; Culver, R.; Swanson, D.; Dunbar, G.; Sharma, A.; Rossignol, J. PAMAM dendrimers advances cross the Blood-Brain Barrier when administered through the carotid artery in C57BL/6J Mice. *Int J Mol Sci.*, **2017**, *18*, 628.
56. Xu, L.; Zhang, H.; Wu, Y. Dendrimer advances for the central nervous system delivery of therapeutics. *ACS Chem Neurosci.*, **2014**, *5*, 2-13.
57. Huang, X.; El-Sayed, M.A. Gold nanoparticles: optical properties and implementations in cancer diagnosis and photothermal therapy. *J Adv Res.*, **2010**, *1*(1), 13-28.
58. Bonoiu, A.C.; Mahajan, S.D.; Ding, H.; Roy, I.; Yong, K.T.; Kumar, R.; Hu, R.; Bergey, E.J.; Schwartz, S.A.; Prasad, P.N. Nanotechnology approach for drug addiction therapy: gene silencing using delivery of gold nanorod-siRNA nanoplex in dopaminergic neurons. *Proc Natl Acad Sci.*, **2009**, *106*(14), 5546-5550.
59. Tsou, Y.H.; Zhang, X.Q.; Zhu, H.; Syed, S.; Xu, S. Drug delivery to the brain across the blood-brain barrier using nanomaterials. *Small.*, **2017**, *13*, 1701921.
60. Saito N, Usui Y, Aoki K, Narita N, Shimizu M, Hara K. Carbon nanotubes: biomedical applications. *Chem Soc Rev.*, **2009**, *38*, 1897-903.
61. Fabbro, A.; Prato, M.; Ballerini, L. Carbon nanotubes in neruogeneration and repair. *Adv Drug Deliv Rev.*, **2013**, *65*, 2034-2044.
62. Skaper, S.D. The biology of neurotrophins, signaling pathways, and functional peptide mimetics of neurotrophins, and their receptors. *CNS Neurol Disord Drug Targets.*, **2008**, *7*, 46-62.

63. Mengying, Z.; Brittany, P.B.; Nicole, L.T.; Kate, H.; Binh, D.; Olesya, M.; Nina, C.; Reyn, A.; Vincent, C.H.; Elizabeth, N. Quantum dot cellular uptake and toxicity in the developing brain: implications for use as imaging probes. *Nanoscale Adv.*, **2019**, *1*, 3424-3442.
64. Serrano, P.A.; Frosch, M.P.; Masliah, E.; Hyman, B.T. Neuropathological alterations in Alzheimer disease. Cold Spring Harb. *Perspect Med.*, **2011**, *1*(1), a006189.
65. Pai, A.S.; Rubinstein, L.; Onytiksel, H. Pegylated phospholipid nanomicelles interact with β-amyloid (1-42) and mitigate its ββ-sheet formation, aggregation and neurotoxicity *In vitro*. *Peptides.*, **2006**, *27*, 2858-2866.
66. Taylor, M.; Moore, S.; Mourtas, S.; Niarakis, A.; Re, F.; Zona, C.; Ferla, L.B.; Nicotra, F.; Masserini, M.; Antimisisaris, G. S.; Gregori, M.; Allsop, D. Effect of curcumin-associated and lipid ligand-functionalized nanoliposomes on aggregation of the Alzheimer's aβpeptide. *Nanomed Nanotechnol.,* **2011**, *7*, 541-550.
67. Cui, Z.; Lockman, P.R.; Atwood, C.S.; Hsu, C.H.; Gupte, A.; Allen, D.D.; Mumper, J.R. Novel d-penicillamine carrying nanoparticles for metal chelation therapy in Alzheimer's and other CNS diseases. *Eur J Pharm Biopharm.*, **2005**, *59*, 263-272.
68. Yang, Z.; Zhang, Y.; Yang, Y.; Sun, L.; Han, D.; Li, H.; Wang, C. Pharmacological and toxicological target organelles and safe use of single-walled carbon nanotubes as drug carriers in treating Alzheimer's disease. *Nanomedicine.*, **2010**, *6*, 427-441.
69. Yarnall, A.; Archibald, N.; Burn, D. Parkinson's disease. *Medicine.*, **2012**, *40*(10), 529-535.
70. Lees, A.J.; Hardy, J.; Revesz, T. Parkinson's disease. *Lancet.*, **2009**, *373*(9680), 2055-2066.
71. Vinogradov, S.V.; Batrakova, E.V.; Kabanov, A.V. Nanogels for oligonucleotide delivery to the brain. *Bioconjugate Chem.*, **2004**, *15*, 50-60.
72. Zhang, Y.; Calon, F.; Zhu, C.; Boado, R.J.; Pardridge, W.M. Intravenous nonviral gene therapy causes normalization of striatal tyrosine hydroxylase and reversal of motor impairment in experimental parkinsonism. *Hum Gene Ther.*, **2003**, *14*, 1-12.
73. Mohanraj, K.; Sethuraman, S.; Krishnan, U.M. Development of poly (butylene succinate) microspheres for delivery of levodopa in the treatment of Parkinson's disease. *J Biomed Mater Res B Appl Biomater.*, **2013**, *101*, 840-847.
74. Chen, T.; Li, C.; Li, Y.; Yi, X.; Wang, R.; Lee, S.M. Small-sized mPEG-PLGA nanoparticles of schisantherin A with sustained release for enhanced brain uptake and anti-Parkinsonian activity. *ACS Appl Mater Interf.*, **2017**, *9*, 9516-9527.
75. Rogver, V.L.; Go, A.S.; Lloyed, J.D.M.; Benjamin, J. E.; Berry, D.J.; Borden, B.W.; Bravata, M.D.; Dai, S.; Ford, S.E.; Fox, S. C.; Fullerton, J.H.; Gillespie, C.; Hailpern, M.S.; Heit, A.J.; Howard, J.V.; Kissela, M.b.; Kittner, J.S.; Lackland, T.D.; Lichtman, H.J.; Lisabeth, D.L.; Makuc, M.d.; Marcus, M.G.; Marelli, A.; Matchar, B. D.; Moy.S.C.; Mozaffarian, D.; Mussolino, E.M.; Nichol, G.; Paynter. P.N.; Soliman, Z.E.; Sorile, D. P.; Sattodehnia, N.; Turan, N.t.; Virani, S. S.; Wong, D. N.; Woo, D.; Turner. B.M.; Heart disease and stroke statistics-2012 update: a report from the American Heart Association. *Circulation.*, **2012**, *125*(1), e2-e220.
76. Donnan, G.A.; Fisher, M.; Macleod, M.; Davis, S.M. Stroke. *Lancet.*, **2008**, *371*(9624), 1612-1623.
77. Schubert, D.; Dargusch, R.; Raitano, J.; Chan, S.W. Cerium and yttrium oxide nanoparticles are neuroprotective. *Biochem Biophys Res Commun.*, **2006**, *342*, 86-91.
78. Peng, T.; Britton, G.L.; Kim, H.; Cattano, D.; Aronowski, J.; Gotta, J.; McPherson, D.D.; Huang, L.S. Therapeutic time window and dose dependence of xenon delivered via echogenic liposomes for neuroprotection in stroke. *CNS Neruosci Ther.*, **2013**, *19*, 773-784.
79. Bates, G.P.; Dorsey, R.; Gusella, J.F.; Hayden, M.R.; Kay, C.; Leavitt, B.R.; Nance, M.; Ross, A.C.; Schaill, I.R.; Wetzel, R.; Wild, J.E.; Tabrizi, J.S. Huntington disease. *Nat Rev Dis Primers.,* **2015**, *1*, 15005.
80. Sandhir, R.; Yadav, A.; Mehrotra, A.; Sunkaria, A.; Singh, A.; Sharma, S. Curcumin nanoparticles attenuate neurochemical and neurobehavioral deficits in experimental model of Huntington's disease. *Neruomolecular Med.*, **2014**, *16*(1), 106-118.
81. Bhatt, R.; Singh, D.; Prakash, A.; Mishra N. Development, characterization and nasal delivery of rosmarinic acid-loaded lipid nanoparticles for the effective management of Huntington's disease. *Drug Deliv.*, **2015**, *22*(7), 931-393.

82. Wenshu, C.; RuBai, Yu, F.L.; Liming, W.; Chunying, C. Selenium Nanoparticles as an efficient Nanomedicine for the therapy of Huntington's Disease. *ACS Appl Mater Interfaces*., **2019**, *11*, 34725-34735.
83. Sanai, N.; Berger, M.S. Glioma extent of resection and its impact on patient outcome. *Neruosurgery*., **2008**, *62*, 753-766.
84. Ozdemir, Y.G.; Pehlivan, S.B.; Sekerdag, E. Nanotechnology methods for neurological diseases and brain tumors: Drug delivery across the blood- brain barrier. Cambridge, MA; Academic Press., **2017**.
85. Gao, H.; Cao, S.; Yang, Z.; Zhang, S.; Zhang, Q.; Jiang, X. Preparation characterization and anti-glioma effects of docetaxel-incorporated albumin-lipid nanoparticles. *J Biomed Nanotechnol*., **2015**, *11*, 2137-47.
86. Kim, S.S.; Rait, A.; Kim, E.; DeMarco, J.; Pirollo, K.F.; Chang, E.H. Encapsulation of temozolomide in tumor-targeting nanocomplex enchances anti-cancer efficacy and reduces toxicity in a mouse model of glioblastoma. *Cancer Lett*., **2015**, *4*, 18.
87. Auffinger, B.; Thaci, B.; Nigam, P.; Rincon, E.; Cheng, Y.; Lesniak, M.S. New therapeutic approaches for malignant glioma: in search of the Rosetta stone. *F100 Med Rep*., **2012**, *4*, 18.
88. Borchard, G.; Audus, K.L.; Shi, F.; Kreuter, J. Uptake of surfactant-coated poly(methyl methacrylate)- nanoparticles by bovine brain microvessel endothelial cell monolayers. *Int J Pharm*., **1994**, *110*, 29-35.
89. Kreuter, J.; Petrov, V.E.; Kharkevich, D.A.; Alyautdin, R.N. Influence of the type of surfactant on the analgesic effects induced by the peptide dalargin after its delivery across the blood-brain barrier using surfactant-coated nanoparticles. *J Control Release*., **1997**, *49*, 81-87.
90. Jain, A.; Jain, A.; Garg, N.K.; Tyagi, R.K.; Singh, B.; Katare, O.P.; Webster, T.J.; Soni V. Surface engineered polymeric nanocarriers mediate the delivery of transferrin-methotrexate conjugates for an improved understanding of brain cancer. *Acta Biomater*., **2015**, *24*, 140-51.
91. Jabir, N.R.; Tabrez, S.; Firoz, C.K.; Zaidi, S.K.; Baeesa, S.S.; Gan, S.H.; Shakil, S.; Kamal, A.M. A synopsis of nano-technological approaches toward anti-epilepsy therapy: present and future research implications. *Curr. Drug Metab*., **2015**, *16*, 336-345.
92. Fang, M.; Xi, Z.Q.; Wu, Y.; Wang, X.F. A new hypothesis of drug refractory epilepsy: neural network hypothesis. *Med Hypotheses*., **2011**, *76*, 871-876.
93. Sab, N.; Archna, P.; Flora, S.J.S. Nanotechnology: A Promising approach for delivery of neuroprotective drugs. *Front Neurosci*., **2020**, *14*, 494
94. Samia, O.; Hanan, R.; Kamal, E.T. Carbamazepine muco-adhesive-nanoemulgel (mneg) as brain targeting delivery system via the olfactory mucosa. *Drug Deliv*., **2012**, *19*, 58-67.
95. Yusuf, M.; Khan, R.A.; Khan, M.; Ahmed, B. Plausible antioxidant biomechanics and anticonvulsant pharmacological activity of brain-targeted βcartone nanoparticles. *Int J Nanomed*., **2012**, *7*, 4311.
96. Kohane, D.S.; Holmes, G.L.; Chau, Y.; Zurakowski, D.; Langer, R.; Cha, B.H. Effectiveness of muscimol-containing microparticles against pilocarpine-induced focal seizures. *Epilepsia*., **2002**, *43*, 1462-1468.
97. Ali, A.; Pillai, K.K.; Ahmad, F.J.; Dua, Y.; Khan, Z.I.; Vohora, D. Comparative efficacy of liposome-entrapped amiloride and free amiloride in animal models of seizures and serum potassium in mice. *Eur. Neuropsychopharm*., **2007**, *17*, 227-229.
98. Hsiao, M.H.; Larsson, M.; Larsson, A.; Evenbratt, H.; Chen, Y.Y.; Chen, Y.Y.; Liu. M.D. Design and characterization of a novel amphiphilic chitosan nanocapsule-based thermo-gelling biogel with sustained in vivo release of the hydrophilic anti-epilepsy drug ethosuzimide. *J Control Release*., **2012**, *161*, 942-948.