**Nanoparticle-based Drug Delivery for the Treatment of CNS Disorders**

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1. ABSTRACT

Disorders of the central nervous system (CNS), particularly neurodegenerative disorders, pose a serious threat to public health and must be thoroughly studied by researchers to protect individuals from them. Over the last few decades, numerous therapy approaches have been used, but their therapeutic success has only partially alleviated the symptoms. Both the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BSCFB) protect the central nervous system (CNS) from harmful substances and present significant obstacles to the delivery of drugs into the CNS for the treatment of CNS complications like brain tumors, autism spectrum disorder, Parkinson's disease, Huntington's disease, Alzheimer's disease, etc. Using nanotechnology to treat neurological illnesses has emerged as an interesting and promising new method that has the potential to solve challenges associated with traditional treatment modalities. Nanoengineered molecules can traverse the BBB, target specific cells or signaling pathways, respond to endogenous cues, operate as a vehicle for the transport of genes, assist nerve regeneration, and support cell survival, among other specialized duties.

**Keywords:** Blood-brain barrier, CNS medicinal, medication delivery, Nanotechnology, Nanomedicine, Nanocarrier

1. INTRODUCTION

The brain is the body's most intricate organ. It plays a role in controlling emotional, behavioral, and cognitive processes. The organ is also a target for a variety of illnesses, from cancer to trauma to neurodegenerative diseases. Injury, infection, tumors, and neurological abnormalities are just a few of the many health issues affecting the brain that are referred to as brain illnesses and disorders. According to the definition, "brain diseases" refers to a collection of medical conditions typically transmissible and frequently brought on by outside factors, such as viruses, bacteria, and so forth [1]. In contrast, "brain disorders" refer to non-transmittable but frequently inheritable medical conditions brought on by disruptions of the normal body structure and functioning as a result of birth defects or genetic malfunctions. From 1990 to 2013, India experienced a burden of mental, neurological, and drug use disorders that was 44% higher than that of several other Asian nations. The medical community should be alarmed by the predicted 23% additional growth of this burden in India by 2025. With 276 million and 11.6% of the world's disability-adjusted life years (DALYs), neurological illnesses are the largest cause of disability, accounting for 9 million fatalities and 16.5% of all deaths worldwide [2]. Brain disorders include ailments like multiple sclerosis (MS), autism spectrum disorder (ASD), and Alzheimer's disease (AD). The electrical, chemical, and physical barriers stop substances like most medications from entering the brain [3]. In the past, prospective medications were dissolved in ethanol, polysorbate 80 (PS-80), and dimethyl sulfoxide in an attempt to improve their penetration and sensitivity across the blood-brain barrier (BBB) [4]. Nanoparticle (NP)-based therapeutics have lately emerged as a prospective therapy for brain disorders because of their straightforward transportability through the BBB and distinctive qualities like tiny size, selectivity, low toxicity, biodegradability, and solubility [5].

Disorders of the central nervous system (CNS) are the leading causes of mortality and disability, which pose a significant challenge to humanity and therefore attract the interests of researchers all over the world. In 2016, neurological disorders were the main cause of disability-adjusted life years (DALYs) [276 million (95% UI 247–308)] and the second biggest cause of deaths [9 million (8.8–9.4)] globally. CNS illnesses are contributing more and more to the global burden of disease [6]. Alzheimer's disease, Parkinson's disease, Huntington's disease, brain tumors, autism spectrum disorder, etc. are just a few examples of neurological disorders that are difficult to diagnose and treat today [7]. Numerous prospective medications have been studied to treat various neurological disorders, but their efficacy is still constrained owing to a variety of difficulties. Delivering substances like medications, nucleic acids, proteins, imaging agents, and other macromolecules to the CNS across peripheral barriers, namely the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB), particularly the BBB, is one of the most frequent challenges [8].

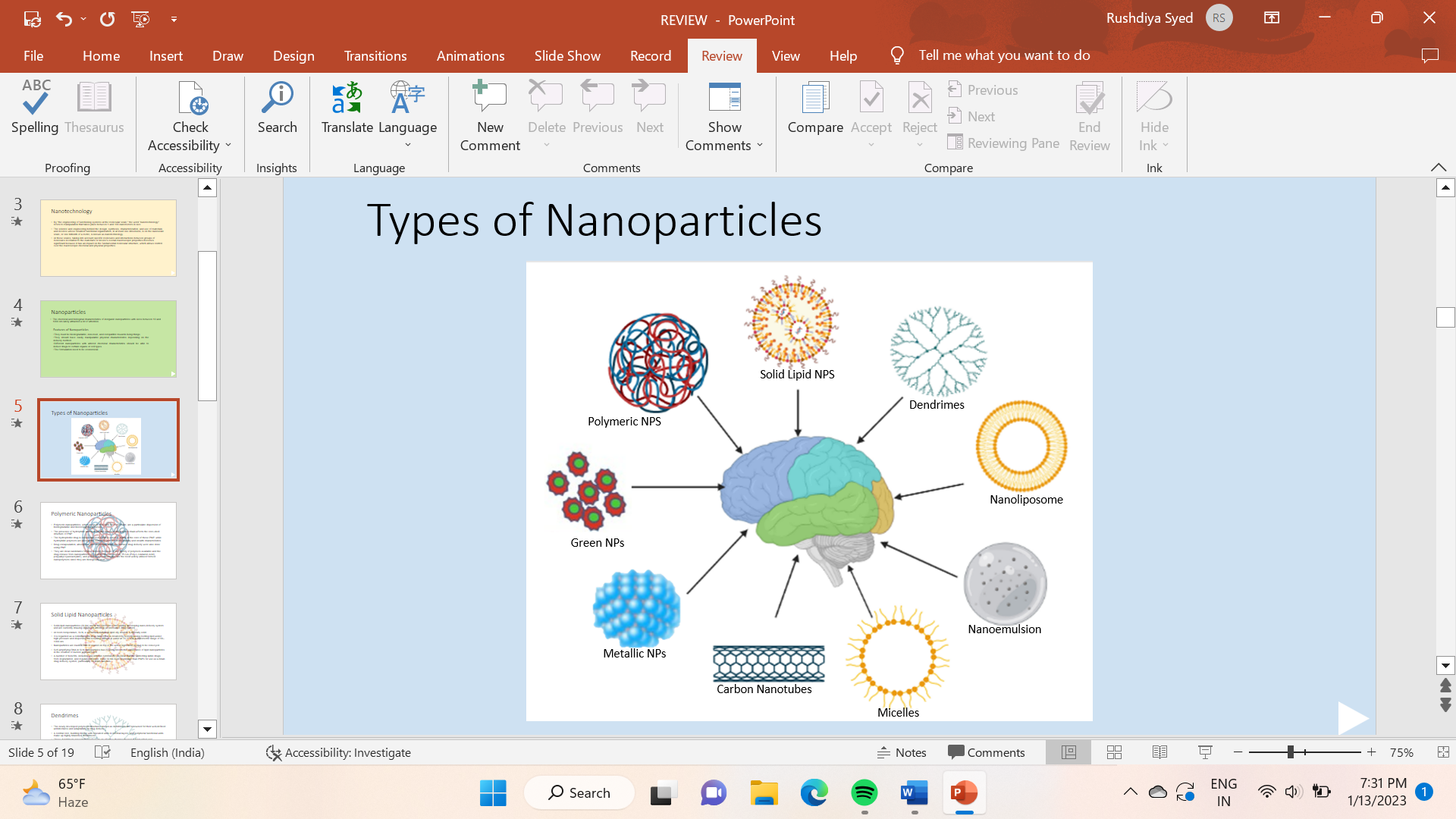
In this review, we discuss the various types of nanoparticles (NPs) and their role in delivering drugs to the CNS. We have also discussed the BBB and its permeability issues, passage strategies for transporting drugs across the BBB, and the targeting mechanism of NPs.

1. REVIEW OF LITERATURE
2. NANOPARTICLES

The word "nanotechnology" refers to manipulation that takes place between 1- 100 nm in size. Nanotechnology is the science and engineering that goes into the design, synthesis, characterization, and usage of materials and devices with the smallest functional organization, in at least one dimension.[10]. A particle is a small entity used in nanotechnology that functions as a complete unit in terms of its attributes and transport. According to size, it may be divided into fine and ultrafine particles. Fine particles have a diameter of 100 to 2500 nanometers, whereas ultrafine particles have a diameter of 1 to 100 nanometers. Like ultrafine particles, nanoparticles have a size range of 1 to 100 nanometers. The chemical and biological attributes of inorganic nanoparticles with sizes between 10 and 1000 nm lately attracted a lot of attention. Numerous characteristics of nanoparticles, such as their high drug-carrying capacity, high stability, controlled release, high specificity, and ability to transport both hydrophilic and hydrophobic molecules, provide considerable benefits over conventional drug administration [11]. The release of drug-loaded nanoparticles to the target region might occur by diffusion, degradation, erosion, or external energy input. Targeted drug delivery most frequently makes use of ceramic nanoparticles and proteins [12]. The main criteria for choosing an efficient method to create various-sized NPs are easy functionalization properties and strong biocompatibility of modified molecules.

1. FEATURES OF NANOPARTICLE

The following promising characteristics should be present in nanoparticles utilized in CNS medication delivery:

1. They must be biodegradable, non-toxic, and compatible with living things.
2. They should have easily manipulable physical characteristics, depending on the delivery method.
3. Drug distribution to specific organs or cells should be made possible by various nanoparticles with modified chemical characteristics [13].
4. The formulation needs to be economical.
5. TYPES OF NANOPARTICLE

**Figure 1: Drug delivery methods based on nanotechnology are used to treat disorders of the central nervous system.**

1. POLYMERIC NANOPARTICLE

Polymeric nanoparticles, which range in size from 10 to 1000 nm, are a particulate dispersion of biodegradable and biocompatible polymers. The presence of hydrophilic and hydrophobic blocks in the polymer chain affects the core-shell structure of PNP [14]. The hydrophobic drug is encapsulated in a dense polymer matrix at the core of these PNPs, while hydrophilic polymers are used in the corona to give the NP steric stability and stealth characteristics. The drug-to-polymer ratio influences drug release levels in addition to molecular weight and polymer makeup. A variety of polymers are available, like PEG (Polyethylene Glycol), PLGA (Poly-L-Glutamic Acid), poly(alkyl cyanoacrylate), and poly(butyl) cyanoacrylate. These are the most widely utilized nanopolymers since they are biologically inert.

Polymeric nanoparticles loaded with quinoline derivatives and doxorubicin are utilized to treat glioblastoma and Alzheimer’s disease (AD), respectively. Similarly, nanosuspensions—a combination of crystalline drugs and non-ionic surfactants—and nano gels (a crosslinked polymer) have depicted superior pharmacokinetic control in CNS disorders [15].

1. SOLID LIPID NANOPARTICLE

Solid-lipid nanoparticles (SLNs) are regarded as colloidal nano drug carriers created by homogenizing melting lipids under high pressure and dispersing the resulting mixture in water at 70 °C with a nanometric range of 50–1000 nm [16]. SLNs demonstrate high physical stability and are easy to manufacture; therefore, they are at the forefront of the rapidly developing nano-delivery system and are currently drawing significant attention as innovative drug carriers [12]. Drugs to be conveyed are loaded onto the top of the nanoparticle [17]. Self-amplifying RNA in SLN nanoparticles has recently shown the significance of lipid nanoparticles in the creation of nucleic acid vaccines [18]. Diminazene aceturate- and quercetin-loaded SLN particles are used to treat human African trypanosomiasis (HAT) and AD, respectively [19]. A similar compound, 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine (DO-FUdR), incorporated into SLN, is used to treat neurological problems [20].

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1. DENDRIMERS

Dendrimes are emerging polymeric structures that are highly branched, and have a central core, building blocks with repeated units in internal layers, and peripheral functional units [21]. The functionality and effectiveness of dendrimers depend on the employed monomer and the intended polymer structure, in addition to the synthesis processes. The High density, high penetration capacity, low dispersity, and peripheral functional group reactivity are additional features of dendrimers that make them an effective therapeutic tool in biomedical and pharmaceutical research. For both hydrophobic and hydrophilic therapeutic molecules, the most often utilized dendrimer drug carriers are polyamidoamine (PAMAM), polypropylene imine (PPI), and polylysine. Drugs can covalently bond with peripherally functionalized dendrimer molecules to generate dendrimer-drug conjugates or physically entrap dendrimers [22].

More than 200 distinct dendrimers have been created and classified into several families based on their structural characteristics, including poly(amidoamine) (PAMAM), poly(propyleneimine) (PPI), poly(L-lysine), poly(carbosilane), and dendrimers containing phosphorus. The PAMAM family of dendrimers is one of the most widely used nanomedicines due to its hydrophilic profile and biocompatible properties and is used in Alzheimer's disease to avoid A-induced toxicity [23].

1. NANOLIPOSOME

These lipid nanoparticles are the most researched bilayer vehicles [24]. Since the name "liposome" covers a wide range of vesicles with typical sizes up to several micrometers, nanoliposomes are also known as "nanoscale bilayer lipid vesicles." To maintain their size within nanometric scales, nanoliposomes provide a larger surface area and an adequate stability profile [25]. Liposomes with neurotrophic compounds are utilized to treat brain diseases [26].

Doxorubicin and (3H)-prednisolone-loaded pegylated liposomes are used to treat autoimmune encephalitis and brain tumors, respectively. (3H) Daunomycin, an antineoplastic agent mediated by the OX26 monoclonal antibody, is conjugated with a liposome and exhibits drug transport to the brain. To treat strokes, heat shock protein (HSP)-encapsulated liposomes are used [27].

1. NANOEMULSIONS

Nanoemulsions are colloidal particulate systems that are either oil-in-water (O/W) or water-in-oil (W/O) based on edible oils, surface-active agents (surfactants), and water, with a size range of 100–500 nm [28]. Their usage as a drug delivery method has recently received a significant promotion to address several issues with traditional delivery systems, including inadequate bioavailability, poor targetability, and BBB penetration. The main factors affecting nanoemulsions' adaptability are the different oils and surface enhancers that are utilized in preparation [28].

For instance, creating nanoemulsions from oils high in omega-3 polyunsaturated fatty acids (PUFA) gives nanocarriers particular abilities to get through biological barriers, including the BBB, and helps to achieve fast medication delivery to peripheral areas, notably the brain. The oral bioavailability of paclitaxel was dramatically enhanced by the nanoemulsion system using pine nut oil [29].

1. MICELLES

Micelles are 80–100nm-thick monolayered spherical lipid nanostructures with hydrophobic ends facing inside and hydrophilic ends facing outward. Due to their tiny size, micelles have a shorter body circulation time than liposomes, making them more quickly transportable substances [12]. In comparison to conventional micelles, polymeric micelles are thought to be more stable, long-lasting, and biodistribution. Due to their nanoscale size, ease of movement to the target region, and low critical association concentration (CMC), these modified micelles exhibit increased target penetration [30].

Numerous attempts have been made to modify the micelles such that a loaded drug with a higher concentration can readily cross the BBB. One such modification involves targeting the receptor on the luminal side of the BBB with polyclonal antibodies against a brain-specific antigen, 2-glycoprotein, or insulin. After being loaded with either a fluorescent dye or the neuroleptic medication haloperidol, these modified micelles were administered intravenously to mice. This boosted the transport of the luminous dye to the brain and dramatically increased the neuroleptic impact of the medicine [31].

1. CARBON NANOTUBES AND FULLERENES

At a nanoscale size of less than 100nm, CNT has outstanding physical, mechanical, and aspect ratio characteristics [32]. High solubility and biocompatibility are displayed by functionalized CNT, and these characteristics often depend on the size, shape, and surface characteristics of the charged molecules. These factors have a significant impact on how therapeutic compounds are internalized by cells. Strategies for CNT functionalization include linking the carboxyl group after oxidation and adding an organic group to the sidewall or tip of the CNT. Additionally, CNTs linked to polymers and dendrimers have improved biocompatibility, increased solubility, and decreased aggregation. Even though acetylcholine-loaded SWCNT (single-wall carbon nanotube) has been examined in the treatment of AD and CNT with stem cell therapy has been employed in the treatment of stroke, very few investigations of the CNT in CNS treatment have been documented. Comparing the administration of amphotericin B alone to the administration of amphotericin B-loaded CNT, lesser aggregation, high solubility with reduced toxicity, and anti-fungal action were observed [33].

The application of nanotechnology in the biosciences and pharmaceutical industries was claimed to be enhanced by the modification of carbon nanohorns and nanodiamonds [12]. Diamond nanoparticles are a vital therapeutic component in the treatment of tumor patches and wound healing. One class of carbon allotropes, defined as 60 connected carbon atoms with 60 vertices and 32 faces, has been specifically recognized as fullerene. The utility of nanosized C60 in drug delivery has been established through significant studies. They were more promising than any other type of nanomaterial due to their antioxidant and radical oxygen-quenching properties [34]. Hydrated C60 fullerene enhances cognitive performance by reducing oxidative stress-induced damage to astrocytes and glial fibrillary acidic proteins (GFAP) [35].

1. METALLIC AND NON-METALLIC NANOPARTICLE

Due to their expanding uses in the area of clinical diagnostics and therapeutics, metallic NPs, including Ag, Au, platinum (Pt), Pd, Cu, selenium (Se), iron (Fe), and their oxides like zinc oxide (ZnO) and iron oxide (Fe2O3/Fe3O4), have attracted substantial attention as prospective DDS. For more than 30 years, metallic NPs have been investigated as effective medicinal drug carriers to increase anticancer effectiveness. Maghemite NPs (-Fe2O3-NPs) and magnetite NPs (Fe3O4-NPs) have proven to be particularly beneficial for therapeutic results, drug administration, and imaging of integrins on tumor cells [36].

Metallic nanoparticles provide several benefits when used as drug delivery systems, including improved stability and half-life of drug carriers in circulation, needed biodistribution, and passive or active targeting to the necessary target location. Green synthesis of MNPs is an emerging area in the field of bionanotechnology and provides commercial and eco-friendly benefits as an alternative to biochemical and physical methods.

When the pH, incubation period, mixing ratio, and temperature are precisely controlled, metallic NPs made from plant extracts are stable and monodispersible. Gold NPs have been produced using curry, mango, neem, turmeric, and guava, among other ingredients. Polyphenols, which are abundant in plant extracts and expedite the decomposition of organic materials [37], and plants that have a significant ability to reduce metal ions both on their surface and in several organs and tissues removed from the ion penetration point can be used to collect metal nanoparticles (NPs).

1. GREEN NANOPARTICLE

Green nanotechnology is emerging as the best choice for production and application to reduce the hazards related to nanotechnology. It became necessary to synthesize the NPs using a green method by keeping in mind the 12 principles of green chemistry to improve the quality of the NPs and make them application-specific with a sustained process of production [38]. Green synthesis uses straightforward, affordable, environmentally benign, and easily accessible raw materials with fewer processes and no hazardous compounds or by-products.

All areas of chemistry are included in "green chemistry," but there is a particular emphasis on chemical compound synthesis and chemical engineering techniques used in industrial settings using natural resources. On the other hand, laboratory investigations are also impacted by the key principles of green chemistry, creating a safer environment. According to sustainable chemistry, or "green chemistry," the use and production of hazardous compounds are reduced during reaction and synthesis. Green chemistry also involves processes for creating renewable materials. The creation of the most efficient reactions, the use of renewable resources for materials and energy, the use of safe solvents or reactants, and the avoidance of waste formation are the key objectives of green chemistry.

The term "green nanotechnology" has been used to describe the process of creating new nanomaterials using the 12 principles of green chemistry to have a positive impact on the economy, society, health, and environment.

For instance, the extract of Corallina officinalis includes proteins with carbonyl groups and polyphenols that may aid in the formation and stabilization of gold nanoparticles [39]. Murraya koenigii leaf extract was used to create and stabilize silver and gold nanoparticles [40].

**Table 1: Different types of nanoparticles and their examples**

|  |  |  |  |
| --- | --- | --- | --- |
| **TYPE** | **SIZE(nm)** | **EXAMPLE** |  |
|  |  | **DRUG** | **DISEASE** |
| Polymeric Nanoparticle | 10- 1000 | Chitosan-coated erythropoietin  PLGA encapsulated NMDA-NRI vaccine | Brain targeting  Alzheimer’s disease |
| Solid Lipid Nanoparticle | 50- 1000 | LDL- cholesterol conjugates  LDL nanoparticles | Alzheimer’s disease, Parkinson’s disease  Epilepsy, stroke, Trauma, Alzheimer’s disease |
| Dendrimes | Diameter range 1.5- 13.5 | Anxiolytic and antipsychotic agents | Psychotic disorder |
| Nanoliposome | Less than 100 | Glutathione encapsulated liposomes  Tempamine loaded liposome | Myoclonus  Multiple sclerosis and Parkinson’s disease |
| Nanoemulsion | 100-500 | Doxorubicin and W198 | Breast cancer cells |
| Micelles | 80- 100 | Doxorubicin  Paclitaxel-loaded copolymer micelle | Cancer  Lung cancer |
| Carbon Nanotubes | Diameter of 3.5- 70 nm | Streptavidin-HRP-bounded SWCNT-annexin conjugates  Stem cell-loaded CNT | Breast cancer  Alzheimer’s disease, Parkinson’s disease, and ischemia |
| Metallic Nanoparticles | 1 nm to a few hundred nm | Silica gold nanoshells  Maghemite NPs | Brain tumor, cancer  Tumor |

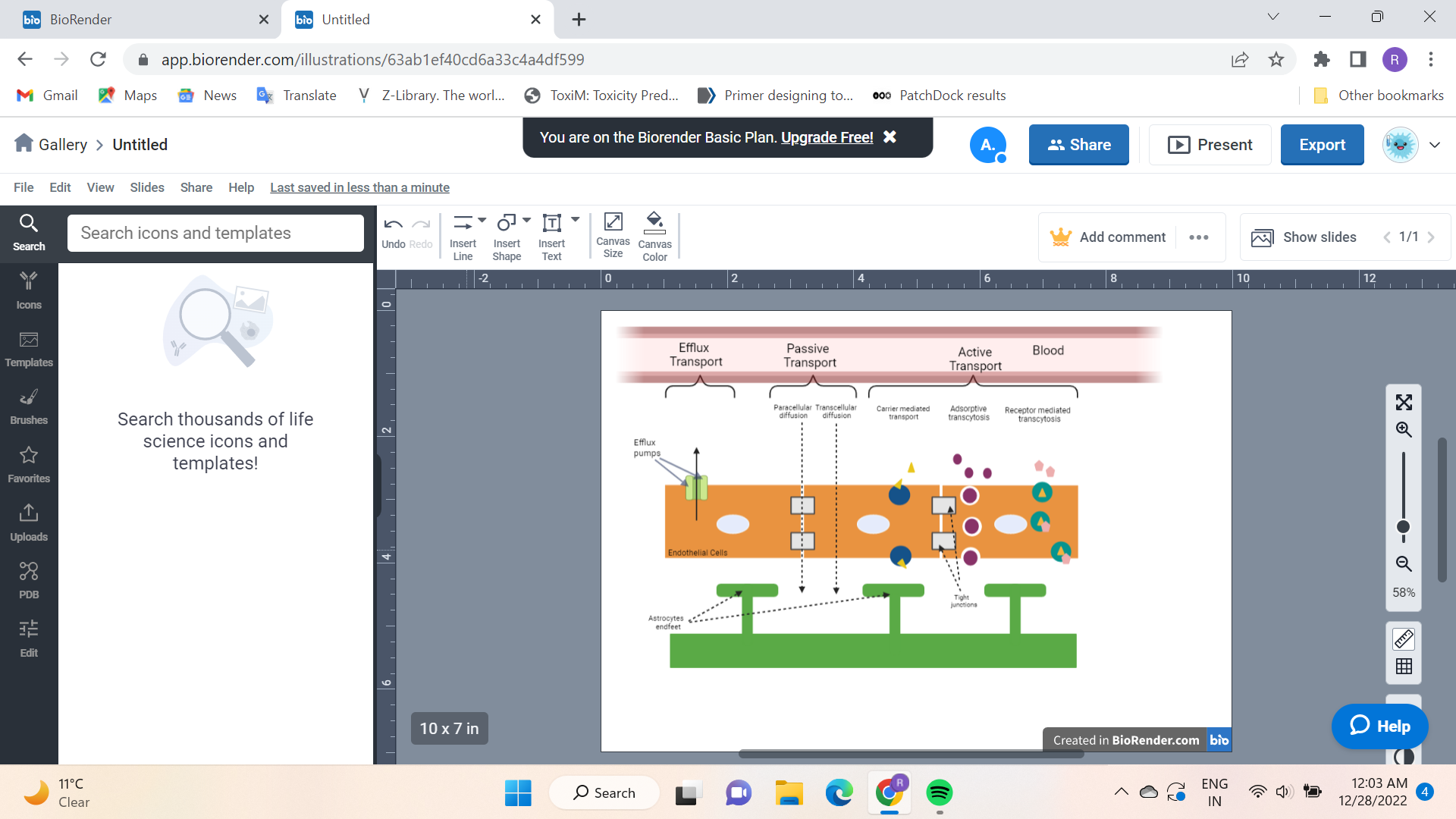
1. ROLE BBB AND ITS INFLUENCE ON THERAPY FEASIBILITY

The human brain, the body's most delicate and intricate organ, is shielded by a barrier known as the BBB. Endothelial cells (ECs) create the BBB, a physical barrier whose primary function is to maintain and control the flow of nutrients and other necessary substances to the brain while preserving its integrity. The tightly packed tight junctions that contact the outer EC membranes and obstruct facile material entry have ECs on their outer and inner surfaces. The BBB serves several important roles, including controlling the flow of chemicals into and out of the brain, maintaining ionic equilibrium, and guarding against the diffusion of circulating agents, neurotransmitters, xenobiotics, and other compounds that may compromise the health of the brain [41].

According to studies, high electrical and chemical [P-glycoprotein (Pgp)], resistance is highly correlated with poor permeability of molecules across the blood-brain barrier (BBB). Cyclic adenosine monophosphate and astrocytes are two important regulators of tight junction activity that have been discovered. The BBB is severely damaged in brain illnesses and disorders, which results in uncontrolled molecule diffusion and additional brain damage. Most prospective drugs do not enter because they do not fulfill the needed parameters, since the BBB blocks the admission of materials based on their size and solubility [42]. Focused ultrasound temporal disruption is one of the methods frequently employed to enhance drug transportation across the barrier, although the mechanism at play and the technique's impact on a disturbed barrier have not yet been fully understood. NPs have recently shown themselves to be effective in this capacity, and as a result, the hunt for a non-disruptive method for medication delivery to the brain has also been given significant emphasis.

1. NORMAL DRUG DELIVERY TO CNS AND THEIR CHALLENGES

The drug should be fat-soluble and have a low molecular weight (400–600 Daltons) for conventional treatment to be successful. This transport can be carried out through invasive, non-invasive, and other methods, but BBB only permits limited penetration of prospective medications. Slow drug action, association or conversion of the drug into non-transporting forms, and lower neuronal absorption are the main causes of therapeutic failures in the brain [43]. Some nervous system catalytic processes also break down drugs that have a general effect or remain inactive in the brain.

1. DIFFERENT MODES OF TRANSPORT ACROSS THE BLOOD-BRAIN BARRIER (BBB)

**Figure 2: Transport mechanisms that traverse the blood-brain barrier**

In contrast to other organs, where there is a range of molecular transport pathways that can pass through endothelial and/or epithelial barriers, the endothelium is much more permeable in brain capillaries due to the smaller number of "windows" between nearby endothelial cells. Since bigger molecules are prevented from traversing the barrier and are instead conveyed into and out of the brain tissue without being identified by particular proteins, the solute stream through the BBB is more regulated than it is in the case of generic capillaries [44]. The way that solute molecules cross the barrier and the methods by which they do so vary depending on the solutes' physical and chemical characteristics as well as the biological structures present in the blood vessel wall. Both passive and active transport are used to transfer molecules across the BBB [45].

Passive transport, also known as passive diffusion, refers to the following non-energetic transport methods:

1. **paracellular diffusion**, which allows hydrophilic compounds to travel between endothelial cells; and
2. **transcellular diffusion**, which allows tiny lipophilic molecules to enter the brain parenchyma by passing through endothelial cells.

By taking into account naturally occurring gradients in biology, passive transport enables the system to attain its intrinsic entropy.

A substance's capacity for passive diffusion is influenced by several intrinsic variables, including pharmacokinetics, hydrogen bonds, and charge. The octanol/water partition coefficient may be used to assess this procedure; for effective passive transport, it should have a value between 10:1 and 100:1. Steroids and diphenhydramine are two examples of commercially available medications that enter the brain via this mechanism [46].

The molecules entering the brain are influenced in part by the paracellular route. This is often true for compounds with extended half-lives, restricted distribution, and potent CNS effects. Examples include erythropoietin and antibodies [47].

The transcellular pathway frequently involves the passive diffusion of gases (e.g., O2, CO2), water, and liposoluble compounds. However, a molecule's ability to pass across membranes cannot just be controlled by lipophilicity. Regardless of lipophilicity, molecules need to have a molecular weight between 400 and 500 Da to pass across the BBB. It was discovered that some lipophilic tranquilizers, like benzodiazepines, may traverse the BBB more quickly than other lipophilic compounds, such as immunosuppressants (like cyclosporine A) [48].

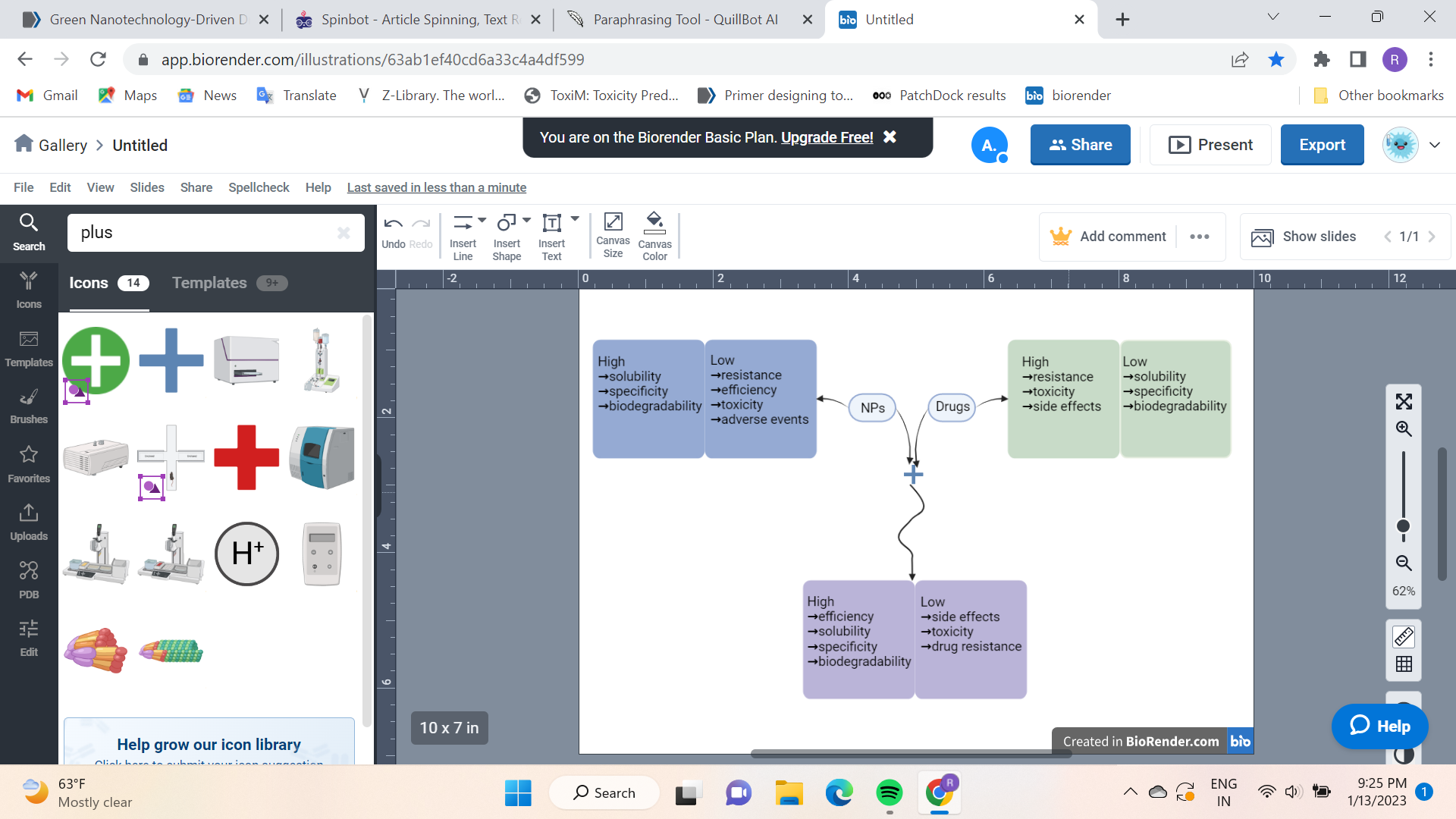
Active transport allows for the energy-dependent transportation of substances into the brain along with their gradient, including nutrients, ions, and endogenous chemicals [49]. Included in this category of transport are (i) receptor-mediated transcytosis, (ii) absorptive-mediated transcytosis for positively charged peptides, and (iii) carrier-mediated transcytosis, which is appropriate for relatively tiny molecules.

Endogenous peptides, including insulin, transferrin, insulin-like growth factor, and the nicotinic acetylcholine receptor, are transported primarily by receptor-mediated transcytosis. These receptors can initiate internalization into cells by selectively binding to appropriate ligands. It is a distinct procedure that removes macromolecules from the luminal side of the brain endothelial cells and delivers them to the brain while reprocessing the receptor back to the luminal membrane [50].

Plasma membrane receptors are not involved in absorptive-mediated transcytosis. Electrostatic interactions between polycationic molecules and the plasma membrane can activate this transit mode (which possesses a negative charge). A non-selective transport pathway through the BBB is produced by particular interactions between the negatively charged endothelial surface and positively charged blood proteins [51].

Capillary endothelial luminal and abluminal membranes provide the route through which nutrients can be transported into the brain by carrier-mediated transport. The blood component is connected with the luminal membrane of endothelial cells, whereas the brain’s extracellular fluid is associated with the abluminal membrane. The BBB is traversed by specialized transporters that allow the movement of amino acids. For instance, the brain may absorb glucose more easily thanks to the glucose transporter (GLUT-1). [52] The System-L transporter carries the energy-dependent amino acids valine, histidine, methionine, and tyrosine.

In the BBB, efflux mechanisms are also present. The P-glycoprotein (Pgp) mechanism is the most well-known and is prone to pumping out unwanted compounds like antibiotics and anticancer medications [53].

1. NANOPARTICLES IN BRAIN DISORDER TREATMENT

**Figure 3 The benefit of drug loading over separate treatments for NPs. Potential medications can be advantageously included into NPs and pharmaceuticals' properties to deliver high efficacy and efficiency. NPs are Nanoparticles.**

1. NPs can more easily penetrate the BBB due to their small size.

The two biggest obstacles to the treatment of brain illnesses and disorders have been crossing the blood-brain barrier (BBB) and the blood-cerebrospinal fluid (CSF) barrier. P-gp carefully regulates the efflux of materials over the BBB; hence, its downregulation is linked to the development of neurodegenerative diseases and tumors [54]. Inhibiting P glycoprotein enhances the BBB-crossing ability of medicines and the effects that result. Rats' P-gp-mediated phenytoin resistance is suppressed by NPs of PBCA (poly (butyl cyanoacrylate)) [55]. Furthermore, a recent study demonstrates that andrographolide, a neuroprotective medication, is more permeable to the BBB when it is enclosed in SL NPs than when it is free. In conclusion, the findings show that by controlling p-gp, NPs can improve the penetration of prospective medications and boost their target ability.

1. **NPs have little toxicity and can be used to increase the toxicity of traditional medications in the cells they are intended to treat.**

The majority of drugs' cytotoxicity has an impact on how well they work therapeutically. NPs significantly reduce brain toxicity as compared to conventional therapies. For instance, intranasal injection of PLGA NPs is claimed to be extremely successful in transporting the mitoNEET ligand inhibitor NL-1 with minimal toxicity in a cerebral ischemia-reperfusion paradigm. Additional research has revealed that the solubility, bioavailability, and sustained release of cytotoxic drugs like amphotericin B (an antifungal drug), thioridazine (an antipsychotic drug), and sorafenib (an anticancer drug) are significantly improved by being encapsulated into nanoparticles (NPs) [56].

As an alternative, NPs can potentially boost the cytotoxicity of traditional medications in the region they are intended to treat, such as tumor cells. In a recent study, it was shown that in an in vitro model, treatment with polyethylene glycol (PEG)-modified silica (Si) NPs increased the cytotoxicity of the anticancer medication 3N-cyclopropylmethyl-7-phenyl-pyrrolo-quinolinone compared to the free drug. Despite the reported potential of NPs, some of these substances, such as Si NPs, may also cause cytotoxicity. It has been demonstrated that the size and porosity of the particle can affect the action of Si NPs [57]. The addition of PEG, commonly known as PEGylation, is a technique that may be used to increase the effectiveness of NPs in addition to the use of particle sizes and shapes that exhibit reduced toxicity. In conclusion, the evidence presented suggests a significant decrease in drug toxicity when some NPs are loaded with the drug as opposed to when the drug is administered freely. Even though encapsulation can occasionally increase cytotoxicity, the effect can be mitigated by PEGylation or by changing the particle size and porosity. A fresh idea called "green chemistry" has emerged in the use of chemical processes that don't employ toxic or dangerous materials.

1. **NPs Enhance the Bioavailability and Solubility of Traditional Drugs.**

Solubility and bioavailability are additional factors that are crucial in determining a drug's effectiveness. The capacity of a medicine to dissolve is known as its solubility, whereas its bioavailability refers to how well it can travel to the systemic blood circulation and, ultimately, the intended location [58]. Drug- or body-related variables can influence drug bioavailability, in contrast to solubility. Age, sex, intestinal pH, genetics, medication dose, and formulation are a few of them. Due to the significance of these characteristics, enhancing one of them might result in higher therapeutic effectiveness and, ultimately, better illness therapy. When silver (Ag) NPs are utilized, methane and ethane are proven to be substantially more soluble in water, and this solubility has been shown to increase with NP mass loading. According to a recent study, putting carvedilol, a hydrophobic medicine, within CS-sodium tripolyphosphate (STPP) NPs boosts the drug's bioavailability and encourages delayed, sustained release of the medication. Similar to this, adding curcumin (a polyphenol and turmeric compound) with PEGylated SL NPs can increase its oral bioavailability and solubility [59]. Numerous additional potential medications, including astaxanthin, asstilbin, sorafenib, and apigenin, have also shown enhanced bioavailability and solubility after being encapsulated in NPs. The aforementioned studies collectively imply that NPs may improve the solubility and bioavailability of less soluble medicines, enhancing their effectiveness.

1. **The Specificity and Biocompatibility of Conventional Drugs are Improved by NPs.**

The drug's biocompatibility and specificity guarantee efficient delivery to the intended spot. Drugs are included in NPs to significantly improve these properties. Recent research demonstrates that chimeric antigen receptor T-cell membrane-encapsulated NPs have excellent biocompatibility and safety in normal cells while having high specificity in targeting tumor cells by recognizing glycan-3 proteins, which are highly expressed in hepatocellular carcinoma cells. The great biocompatibility and selectivity of the NPs were further supported by the finding that biomimetic gold (Au) NPs stabilized by seaweed extracts were fatal in breast cancer cells MDA-MB-231 at a dose of less than 45 μg/mL while having no effects on human embryonic kidney cells at 150 μg/mL. Additionally, compared to common antibody-conjugated magnetic micron beads, which only exhibit about 20% specificity and sensitivity, specific antibody-loaded iron oxide (IO) NPs have high sensitivity and specificity, greater than 95 and 90%, respectively, in capturing amyloid (A) and Tau proteins in the serum and CSF-mimicking samples and about 80–90% in human whole blood samples, indicating the technique's potential as a biomarker for dementia [60]. Overall, the information suggests that NPs are highly selective and biocompatible and may be utilized to more effectively deliver medications to the desired areas.

1. USE OF NANOPARTICLES IN THE TREATMENT OF MANY CNS DISORDERS

The potential use of different kinds of nanomaterials and nanoparticles in the treatment of different kinds of CNS disorders

1. ALZHEIMER DISEASE

A frequent form of dementia known as AD is characterized by age-related, progressive neuronal degeneration that reduces cognitive function and other neuropathological characteristics. One of the pathogenic characteristics linked to the development of neurodegenerative illnesses, such as AD, is the buildup of Tau proteins [61]. According to a recent study, protein-capped cadmium sulfide and IO NPs may efficiently prevent Tau proteins from polymerizing and fibrillizing, with inhibition rates of 63 and 49%, respectively. The accumulation of Aβ, which causes a decrease in Aβ-binding ability and plaque development, is another pathogenic aspect of AD. A serine/threonine kinase known as GSK-3 has been linked to the development of Aβ, hyperphosphorylation of Tau proteins, and the progression of AD. In contrast, treatment of 5XFAD mice with PLGA NPs loaded with vitamin D-binding protein reduces cognitive deficits by preventing Aβ binding and accumulation. By encouraging anti-inflammatory responses and enhancing antioxidant status, Au NPs have also been shown to generate cytoprotective benefits in rat models of AD. Additionally, it has been demonstrated that surface-coated Au NPs can decrease Aβ aggregation; however, the impact depends on the NPs' diameter and surface chemistry. The Aβ fibrillization and related neurotoxicity in the AD model are reported to be considerably reduced by Au NPs with negative surface potential. Additionally, a recent study indicates that smaller Au NPs are more effective than bigger ones at suppressing Aβ fibrillization [62]. The information above suggests that NPs can be utilized to more efficiently and effectively transport medications that target peptides that are dysregulated in AD, such as Aβ.

1. PARKINSON DISEASE

One of the most prevalent forms of neurodegenerative disorders, PD, is very prevalent in people over the age of 50. Motor and non-motor abnormalities are symptoms of the condition, which is defined by the loss of substantia nigra dopaminergic neurons and the development of Lewy bodies (LBs) [63]. Environmental and genetic variables are both very important in how the disease develops. By promoting neuronal loss and increased vulnerability to stressors, the LBs' synuclein aggregates help the illness proceed. Additionally, research demonstrates the efficacy of polymeric NPs loaded with microRNA-124 in treating PD symptoms and correcting motor deficits. Treatment with iron (Fe) chelation NPs modified with zwitterionic poly(2-methacryloyloxyethyl phosphorylcholine) and HIV-1-transactivating transcriptor to delay iron saturation in the blood and increase iron lifetime can reverse Parkinson's disease (PD) symptoms more successfully than individual treatments. Further research shows that administration of Au NPs to PD mice generated by alkaline reserpine can effectively restore behavioral deficits, enhance antioxidant status, and prolong neuronal life. In addition, compared to pure levodopa, the main medication used to treat PD, the treatment of PD-induced mice using nano dopamine medicines also improves motor deficits with low toxicity. Similar to this, metformin-loaded polydopamine nanoparticles (NPs) support anti-inflammatory, anti-apoptotic, and antioxidative properties linked to the proteolytic degradation of phosphorylated serine 129 of the synuclein protein induced by targeting a histone-lysine N-methyltransferase enzyme known as the enhancer of zeste homolog 2 [64]. Selegiline CS NPs, borneol and lactoferrin comodified NPs, resveratrol NPs, and Cerium NPs are some more NPs and nanodrugs that have been shown to offer substantial promise in the treatment of PD by controlling oxidative stress and inflammation. In conclusion, because of their role in the control of inflammation, oxidative stress, apoptosis, and -synuclein activities, and the downstream consequences in motor and non-motor dysfunctions, NPs and nanodrugs show tremendous promise in the treatment of PD.

1. HUNTINGTON’S DISEASE (HD)

HD is a neurodegenerative illness that progressively worsens over time and has an autosomal dominant genetic basis. Genetically, the condition is caused by a mutation in the huntingtin gene, which can be seen by the expansion of polyglutamate repeats in exon-1 and the subsequent functional abnormalities in the downstream protein caused by posttranslational mechanisms [65].  Se, an important metal with defenses against cytotoxicity and redox imbalance, is significantly reduced in the brain autopsies of HD patients. On the other hand, a recent study found that Se, iron, and chromium are three important components that are noticeably higher in blood samples from HD patients when compared to healthy people. Se NPs may be useful in treating HD because, in Caenorhabditis worms, therapy with modest concentrations of the substance improves oxidative status and prevents the aggregation of huntingtin proteins, which reverses brain state. Similar to this, data suggest that TiO2 NPs can accelerate the oxidation of methionine on the N-terminal domain of the mutant huntingtin protein, resulting in the formation of sulfoxide and preventing the protein from aggregating. Furthermore, research suggests that treatment of HD mice with polymeric NPs modified with glycopeptides loaded with cholesterol can cure behavioral and cognitive deficits [66]. When the nose-to-brain transport is examined, it is shown that liposomal NPs are successful in delivering cholesterol through this pathway in HD mice models, demonstrating their promise for treating HD. The information presented above supports the neuroprotective properties of NPs and their potential for treating HD by focusing on critical pathways that contribute to the disease's development.

1. BRAIN TUMOR

Malignant and benign tumors that affect the brain are referred to as brain tumors. Because of the intricacy of the brain, benign tumor development, as well as metastatic disease, might result in negative effects [67]. Cognitive impairment is linked to the disease's development. The disease's pathophysiology is not well understood, and it is currently unknown how to treat it. Nevertheless, several investigations have documented the therapeutic benefit of NPs in the delivery of promising anticancer medications. By employing polymeric NPs to deliver small interfering RNA to numerous genes, including sodium-potassium (Na-K)-chloride cotransporter 1, yes-associated protein 1, roundabout homolog 1, and surviving glioblastoma cell growth and migration may be dramatically and selectively inhibited [68]. It has been demonstrated that the combination of ganciclovir and modified polymeric NPs loaded with herpes simplex virus type 1 thymidine kinase may significantly decrease the viability of glioma cells while increasing the survival of mice with tumors [69]. The aforementioned information supports the use of NPs for brain tumor-specificness and medication delivery.

1. AUTISM

American psychiatrist Leo Kanner originally identified autism as a neurodevelopmental condition in 1943 that is characterized by poor communication and recurrent stereotyped behaviors [70]. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-5's diagnostic criteria for ASD have recently undergone considerable revisions. Several diagnoses have been integrated into the one-dimensional diagnosis of ASD. Additionally, there are three ASD diagnostic criteria: (1) qualitative social interaction deficit (2) in communication, and (3) confined repetitive, stereotyped, and repeating behavioral patterns, interests, and activities have been constructed two domains  (1) Continuing issues with social engagement and communication (2) confined, recurrent patterns of action, passion, or interest.

Since then, autism has been classified more broadly as an autism spectrum disorder (ASD), which encompasses a variety of symptoms, abilities, and levels of impairment. There is a need for creating cutting-edge therapy alternatives for the illness despite the absence of worldwide data. ASD is a developmental disorder marked by issues with behavior and communication. NPs based on titanium dioxide are among the most widely manufactured and utilized NPs (TiO2) [71]. Although TiO2 NPs are often thought to be harmless and non-toxic, several studies have suggested that the rising use of nanoscale TiO2 particles may pose health risks [72]. Nanoparticle has been used in autism spectrum disorder but not much research has been done. This field of study has not been investigated.

Only a little amount of study has been done that revealed a negative side of the nanoparticle. Mice exposed to titanium dioxide (TiO2) NPs showed behavioral impairment in their offspring that is similar to ASD; the substance has no physiological consequences [73]. Briefly stated the evidence above suggests that NPs can deliver medications; however, further research is required to determine the nanoparticle effects to treat autism.

CONCLUSION

The World Health Organization and the Global Burden of Disease studies estimate that each year, neurological illnesses result in 9 million deaths and 276 million impairments worldwide. These instances are also anticipated to grow significantly shortly. The BBB, a physiological interface that restricts the entry of different therapeutic agents into the brain and is one of the most important problems in the treatment of CNS illnesses, makes it difficult to treat and manage CNS disorders. Therefore, brain-targeted medication carriers are required to treat CNS diseases. Due to its unique properties, such as its nanoscale size, high surface-to-volume ratio, selectivity, sensitivity, surface modification, charges, and stability, the nano-scaled drug delivery system has attracted researchers from various fields of biomedical science, particularly neuroscience. This is because traditional drugs cannot cross the BBB and are less effective than their nanoscale counterparts. The use of nanotechnology in the therapy and diagnosis of central nervous system conditions is a novel and exciting concept.

Only a small number of medications have received FDA approval and/or are undergoing different phases of clinical testing. Because the possible negative effects of these methods on people are still mostly unclear, there aren't many clinical trials for nano-based treatments for central nervous system disorders. Rigid validation standards for both in vitro and in vivo protocols are needed from the bench to clinical trials since the area of nanomedicine is still relatively undeveloped and underexplored. Large-scale production necessitates innovation from engineers, chemists, and other experts in the industry. Similarly, regulatory laws must be adjusted to simplify access to trials and patients. More study is needed to comprehend the safety issues with nanoparticles and prove their therapeutic uses.

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