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REVIEW ARTICLE

Current Avenues in Nanotechnology-based Drug Delivery System for Brain Targeting

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ABSTRACT
The development, production, and characterization of materials and devices with functional associations at the nanometer scale are all possible with the help of nanotechnology, which promises to "smart" therapeutic approach. The targeted transportation of medications as well as other biomolecules through the blood brain barrier, the toughest barrier in vivo, is one area where nanoscience may have a big therapeutic potential in neuroscience. Consequently, many approaches to enhance the transport of several anticancer medications, aptamers to this tissue were suggested. The article briefly discusses the BBB's condition as well as several brain pathologies such inflammatory, stroke, as well as neurological illnesses. This review's initial section tries to explore the methods created to get around the Blood brain barrier as well as transfer medications to the brain. In the most important section of the review, the need for nanotechnology as well as advances are specifically discussed, demonstrating their potential as a non-invasive technique that overwhelms the BBB's defining qualities in the drug - delivery with the potential to attack specific neural tissue while reducing peripheral cytotoxic activity.

Keywords; *Blood Brain Barrier, Neuroscience, Nanotechnology, Brain targeting, Nano particle.*

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INTRODUCTION

Since ancient times, plant-based natural remedies have been widely used as therapies for various of ailments. Modern drugs are mostly produced from plants, based on practices and traditional knowledge [1,2]. Natural compounds with a wide range of molecular backgrounds can be used as a starting point for new drug development. A contemporary trend in medication formulations based on natural products development is research into producing synthetically accessible lead molecules that mimic their counterpart's chemistry [3]. Biological and chemical capabilities with macromolecular uniqueness, Chemical variety & Low toxicity are all characteristics of natural items. So, they're promising leads the way in search for new drugs [4]. Computational research has also supported the creation of next-generation drug technologies including drug development and delivery that is based on a patient's specific target. Nanotechnology has been shown for bridge gap between physical and biological sciences by utilizing nanophases & nanostructures in a number of scientific domains [5], especially in nano-based drug delivery applications and nanomedicines, where such molecules are of particular value [6,7]. Nano-delivery systems for targeted therapy could also lead to improved outcomes. An indirect decrease in side effects associated with a variety of medications, as they should. Drug interactions with non-target tissues should be avoided or greatly reduced. A direct statement resulting from the reduced number of unwanted drug interactions so dosage would be reduced. As a result of the drug being required in order to treat condition so resulting in an overall decrease in cost [8-10]. Since the brain has a highly effective protective barrier, delivery of medication to this tissue is difficult. 95 percent of genuinely valuable bioactive molecules are kept out of the brain by the same systems that keep foreign substances out. The major barrier to active chemicals moving from the circulation to the brain is the BBB. It is present at

region of the brain's vessels, where pericytes, endothelial cells astrocytes and microglia all converge [11]. Nano is the one billionth in the world of nanotechnology. Nanotechnology deals with a wide spectrum of structures ranging in size from billionths a metre to billionths a metre. As a result of the notion, the size and shape of materials now define their function. This distinguishes nanoscience from other traditional technologies that have a role to play in the nanometer range. The dimensions of biomolecules such as DNA and proteins are measured in the range of 1 to 100 nm [12-14]. Nanotechnology-based materials have many potentials for medicinal and pharmaceutical applications, including medication targeted therapy due to their size-related features. Pharmacokinetics and biopharmaceutical characteristics are inadequate in 95 percent of all novel drug candidates currently. That's why effective methods for drug administration must be created to transport the drug molecule selectively towards the goal spot while avoiding harming healthy tissues and organs [15-18]. Alzheimer's disease, Brain cancer, stroke, multiple sclerosis and Parkinson's disease are some of the popular diseases, frequency for the same is increasing as population gets older [19]. Non-invasive or Invasive or delivery methods for therapeutic medications towards the brain are available. The administration methods for non-invasive technique are depend on the anatomic structures of the brain cells, capillaries, and extracellular milieu, as well as the directed transport of fluids transversely the brain, with the nasal and systemically administration routes being the most common [20]. This article concentrated on various nanocarriers used for therapeutic targeting in the brain for a few Central Nervous System illnesses. The use of these NCs in brain illnesses, in addition to pathophysiology of blood brain barrier is also highlighted. Along with this, most recent advances in nanotechnology-based delivery methods combining liposomal systems, polymeric nanocarriers, polymeric micelles, dendrimers, gold nanoparticles (Au-NPs) and quantum dots are thoroughly explored. The therapeutic implications for brain targeting and optimal characteristics of nanocarriers, were also thoroughly investigated.

THE BRAIN'S PATHOPHYSIOLOGY:

With its extended and branching structure, intricate interconnections, and scattering qualities, the brain is the body's most complicated organ in terms of form as well as number of nerve cells [21]. BBB is made up of many types of endothelial cells of the cerebrovascular system, pericytes, neurons and astrocytes. Cognitive, sensory dysfunctions and motor are all common in patients with brain trauma [22]. The parenchyma suffers acute and irreparable injury causes irreversible and sudden primary brain damage, with subsequent brain damage that occur at slower rate, giving a window for effective treatments. Secondary brain trauma is characterized by mitochondrial malfunction, oxidative stress, axon degeneration, excitotoxicity as well as neuronal and glial apoptosis [23]. The BBB is disrupted by a brain injury, whether it be traumatic brain injury or hemorrhagic stroke or ischemic stroke [24]. Tight junction complexes, which are composed of specialized endothelial cells that border BBB, come together to create the hurdle. This acts as a physical boundary to intercellular transport while simultaneously supporting the BBB's high trans endothelial electrical resistance [25].

TRANSCYTOSIS AND PARACELLULAR TRANSPORT:

Two main protocols should be examined when considering the BBB's works: Transcellular and paracellular transport. The brain's CSF "sink" enables a more precise constitutive equilibrium and intracranial mass are described [26]. Because of the intimate connections between the brain and blood intercellular transit is controlled. [27]. Unidirectional transcytosis is in polarized cells, the migration of larger molecules from the apical to the basolateral plasma membrane. This process includes endocytosis, intracellular vesicular trafficking, and exocytosis [28]. Because of specific tight junctions, the CNS barrier properties were preserved with low transcytosis levels. Therefore, this finding, it's now obvious that BBB transcytosis suppression is a live process, with CNS-specific genetic programmers trying to keep the barrier intact [27]. The transcytosis receptor is found in endothelial cells in the brain [29] The mechanism of transcytosis and paracellular transport as shown in fig 1.

THE DIFFICULTIES OF DESIGNING CNS MEDICATION:

Many CNS illnesses do not have treatment options. The lot of small medicines may not pass the BBB. Exclusively 5 percent of the medications in the comprehensive medicinal chemistry database (about 7000) affect the CNS, but some CNS effective pharmaceuticals only cure insomnia, depression etc. According to research, just 12 percent medications seem to be effective with in CNS, while about 1 percent among all pharmaceuticals seem to be effective as in CNS treating disorders apart from aversive diseases [11].

RESTRICTIONS FOR MEDICATIONS TO PENETRATE WITHIN CNS:

Pharmaceuticals can be carried via the BBB in two ways: passively or actively as shown in table 1.

PASSIVE TRANSPORTATION:

The primary parameters that interfere in passively transport over the BBB are medication ionization, molar mass, hydrophobicity, and binding of proteins. When acidic substances ionize, their transportation across the BBB is reduced. Basic groupings of ionization have no impact. The molar mass of a medication is inversely attributed to its transit over the BBB. It's been established, at values more than 600 Daltons, molar mass could be a determining constraint. Hydrophobicity is probably amongst the most critical elements influencing medication absorption in the brain. The transportation of a medication over the BBB is often proportional with its lipid solubility. Log P values ranging from -0.2 to 1.3 have been reported as ideal for cerebral transportation. Of those limits, brain transport is determined by flow of blood and the coefficient of permeability [11].

ACTIVE TRANSPORTATION:

Transport over the BBB will be more or lesser than predicted based on physicochemical features for specific medications. An increased proportion of transport might be attributed to assisted or active transportation. If the percentage of transport is slow, outflow proteins are sometimes implicated [11].

DRUG DISTRIBUTION TO THE BRAIN: STRATEGIES:

Capacity of biologically active molecule to permeate lipid membranes is essential for drug diffusion from blood into the brain. The assumption has resulted in the creation of a number of approaches to traverse the BBB, including both invasive and non-invasive procedures [11].

INVASIVE METHODS:

BBB DISRUPTION:

The first method for bypassing the BBB for medicinal purposes by Neuwelt, and the same was first to be used in humans [30]. The objective behind this treatment was to inject mannitol solution into the neck arteries to temporarily break down barriers. Such high sugar content in brain capillaries causes endothelial cells to lose water, causing them to shrink and tight junctions to open. Medications that would usually cross the BBB easily diffuse during the 20–30 minutes' duration of effect [31]. Transient elevations in intracranial pressure, Physiological stress, and unanticipated transfer of antineoplastic drugs to typical brain areas are all unwanted adverse things of this method in people. Alteration of biochemistry technique causes a specific increase in anticancer drug penetrability through blood–brain tumor barrier (BBTB) without harming normal BBB [32] Transportation routes for crossing blood brain barrier are shown in fig 2.

DIRECT DRUG DELIVERY:

Medication was directly administered through intracerebral as well as intraventricular channels in a clinical experiment, a subcutaneously implanted plastic reservoir in the scalp and an output catheter connecting it to brain's ventricles [33]. Unfortunately, several issues exist, including insufficient drug concentration reaching specified region, interstitial fluid flow that has been secreted working in opposition to drug permeation that is diffuse, and a CSF's high turnover rate, which allows injected drugs to be returned inside the bloodstream [34].

Intracerebral drug delivery varies from systemic administration of medications with respect to pharmacokinetic characteristics defining concentration of brain tissue since the available dosage reaching the 100 percent of the target organ [35, 36].

CONTROLLED RELEASE SYSTEMS OF INTRACEREBRAL IMPLANTATION:

To administer medication delivered straight to the brain interstitium, polymeric devices that distribute large amounts of medicine to an intracranial target in a sustained way over prolonged durations can also be utilized. The following factors determined the fate of a medicine administered via biodegradable polymer: (a) Degradation, metabolism, and penetration through capillary networks are all used to eliminate drugs from the brain; (b) Rates of local binding and internalization and (c) Diffusion and fluid convection are used to transfer drugs [37]. GliadelTM was FDA-approved after clinical studies in glioma patients [38]. Benoit used stereotactic implantation microspheres made from biodegradable materials to test a new idea of medicine targeting into the CNS [39]. Micro particle implantation, unlike large implants, does not involve open surgery. The ability of neurotrophic factor produced from glial cell lines [40,41] and 5-fluorouracil (5-FU) [42,43] microencapsulation to survive in neurological diseases and brain malignancies has enabled for local administration. Microspheres were inserted in the tumour following an extensive macroscopic surgical intervention in a phase I pilot research exploring the targeted as well as prolonged administration of 5-Fluorouracil to 8 patients with glioma. [44]. This invasive technique, however, has been related to a higher risk of infection as well as a high neurosurgical cost [45].

NON-INVASIVE TECHNIQUES:

Chemical or biological delivery mechanisms can be used for non-invasive delivery.

CHEMICAL TECHNIQUES:

The prodrug strategy is applied in chemical processes to boost certain physiological properties that were lacking such as vascular fluidity as well as membrane solubility. In most cases, an enzymatic cleavage is employed to transform the inactive form to the active form. A lipid moiety, such as a glyceride, phospholipid, fatty acid, might be used to bind the medication to a CNS prodrug. A range of acid-containing medications, including levodopa, have been examined using such prodrug approaches [36]. Poor selectivity and tissue retention are two more concerns with prodrugs. Increasing lipophilicity boosts cytochrome P450 and other enzymes' oxidative metabolism. Greater hydrophobicity can enhance BBB diffusion, leading to greater tissue load and absorption into adjacent tissues [46].

BIOLOGICAL TECHNIQUES:

Biological approaches include combining a medication using antibodies that can then be directed towards an antigen present on or inside the target organs. Antibodies addressing the transferrin receptor, such as R17-217 MAb, OX26, 8D3 MAb, have been discovered for being capable of receptor mediated trancytosis throughout the BBB of mouse via the endogenous TfR. Tumor-specific antigens, for example, are uncommon in cancer chemotherapy; tumor-associated antigens can be distributed throughout the body, not just in the target tissue. Other biological methods of targeting include the use of ligands like lectins or sucrose that can target certain cell surface receptors [46].

DIFFERENT METHOD OF ADMINISTRATION:

Another method for delivering CNS medications is intranasal administration, which enables for rapid absorption into systemic circulation while bypassing stomach and liver first-pass metabolism. This method has been proved to be an effective and safe substitute for parenteral medicine [47].

A recent study investigated low-frequency technology's viability magnetic resonance (MR) image-guided focused ultrasound as a non-invasive technique for temporarily piercing the blood-brain barrier (BBB) in specific areas [48].

APPROACHES TO CROSSING BLOOD-BRAIN BARRIER USING NANOTECHNOLOGY:

As a result of coordinated interdisciplinary activities, nanotechnology growth will lead to unique techniques for the identification and treatment of brain illnesses and insights into the activities of neural circuits [49]. It's highly important as a result of present approaches' limitations for delivering medications via the blood-brain barrier to the central nervous system [50]. To target brain locations, nanotechnology-mediated medicine delivery systems utilize both selective and non-specific approaches [51].

ORGANIC NANOMATERIALS

POLYMERIC NANOPARTICLES

As nanoparticles offer properties of adequate delivery of drug, such as targeting efficiency and controlled drug delivery, they have been widely utilized in creation of drug delivery carriers that can pass through BBB. Furthermore, they can prevent reticuloendothelial phagocytosis, which improves medication concentration in the brain [52]. For effective blood-brain barrier bridging, inorganic and polymeric nanoparticles have been investigated. The poly (lactide-co-glycolic) acid is utilized as a precursor for nanoparticle therapeutics synthesis encapsulation of drugs for cancer and Alzheimer's disease of brain treatment has been the topic of recent research. In vitro research revealed that using polymeric nanoparticles improved medication distribution to the brain, resulting in lower inflammation, oxidative stress and plaque load via increased curcumin distribution for treatment of Alzheimer's disease [53], and efficient Internalization of Doxorubicin in human glioma cells, resulting in cancer cell cytotoxicity [54]. Moreover, an in vivo study using poly (lactide-co-glycolic) nanocarriers to transport boldine and cisplatin, an antioxidant drug, found efficient therapeutic use of target-specific delivery in brain cancer treatment [55]. Docetaxel can now be given in order to treat brain metastases thanks to the invention of a system of nanoparticles having penetrating amphiphilic polymer-lipid type [56]. The nanoparticles outperformed saxagliptin suspension in terms of plasma stability, premature release, and brain transport in Vivo studies [57].

LIPOSOMES

Liposomes are synthetic spheres made up of single amphiphilic lipid bilayers that can encapsulate medicinal substances which included vaccines, nucleic acids, proteins and drugs. As a result, it is frequently used as the drug delivery systems which increase safety and efficacy of medicines [58].

Drugs which are Anti-cancer such as 5-fluorouracil, doxorubicin, erlotinib, methotrexate & paclitaxel have been delivered via liposomal formulations in several studies [59]. There are a few formulation options that can be used to improve the effectiveness of liposome transit through the blood-brain barrier [60]. Liposomes have also been used as gene therapy carriers. Both the delivery of oligonucleotides for brain cancer therapy using mannitol to disrupt the blood-brain barrier and the delivery of liposomes

functionalized with transferring receptor targeting and penetration for enhanced cell penetration and efficient delivery of nucleic acids for the treatment of brain diseases have been reported [61].

DENDRIMERS

Dendrimers are type of synthetic macromolecule that has structure like tree, particular encapsulation capabilities, and predetermined molecular weights [62].

Dendrimers are employed as strategy based on nanotechnology to pass the blood-brain barrier to treat brain neuro inflammation, neurodegenerative illnesses, stroke, cancer and circulatory arrest. Glioma homing peptides and Poly (ethylene glycol) associated polyamidoamine dendrimers were developed to target glioblastomas, revealing enhanced tumor penetration in vivo results [63].

MICELLES:

Micelles are amphiphilic compounds with particles ranging in size from 5 to 50 nanometres in diameter. At certain concentrations and temperatures, micelles form spontaneously in aqueous solutions [64]. Amphiphilic molecules self-assemble with hydrophilic/polar head facing hydrophobic/non-polar tail and the outer surface forming core in this approach. Micelles have attracted a lot of attention because of their ability to transport molecules that aren't very water soluble while simultaneously providing chemical and physical stability, regulated and prolonged release, and increased therapeutic bioavailability [65].

Micelles have been employed as nanocarriers to transport curcumin for treatment of Alzheimer's disease and glioma in recent studies [66]. Micelles containing contrast ants could also be used to image neuro inflammation [67] and ischemic stroke damage [68] using magnetic resonance imaging.

INORGANIC NANOMATERIALS:

GOLD NANOPARTICLES:

The use of therapeutic macromolecules to functionalize gold nanoparticles has been studied extensively neurodegenerative diseases' treatment. Parkinson's disease and Alzheimer's disease have been examined in vitro, with better blood-brain barrier permeability using L-DOPA functionalized multi-branched nanoflower-like gold nanoparticles and gold nanoparticles functionalized with -amyloid specific peptides [69].

Another study used polyethylene glycol-coated gold nanoparticles and citrate and to visualize changes in vasculature of the cortex associated with blood-brain barrier disruptions. The nanoplatforms' properties were validated using multi-photon luminescence imaging to monitor vascular anatomy and physiology in brain disorders when nanoparticles were fed to animals with stroke models. Drug delivery and early detection of blood-brain barrier dysfunction could both benefit from nanoparticles having a diameter of 5 nm or less [70].

SILICA NANOPARTICLES:

The ability of surface modified fluorescent silica nanoparticle derivatives to attach various types of molecules to the core has showed promise for use as nano-vehicles for brain drug delivery [64]. The process of receptor-mediated transcytosis of these nano systems was improved by attaching lactoferrin to the surface of polyethylene glycol-coated silica nanoparticles, with a maximum transport efficiency identified for nanoparticles with a diameter of 25 nm. As a result, drugs and imaging probes could be transported across the blood-brain barrier using these nano systems [62].

It has been suggested that silica nanoparticles could be used to deliver nootropics such as pyridoxine, piracetam, pentoxifylline which have been created to promote blood-brain barrier permeability. In comparison to unencapsulated medicines, which were not located in the mice's brains, the efficacy of silica nanoparticles as drug nanocarriers has been shown [61].

To improve the transcytosis process across the blood-brain barrier, Polylactic acid-coated mesoporous silica nanoparticles conjugated with a ligand peptide of the low-density lipoprotein receptor were used to deliver resveratrol, a therapeutic agent for the removal of excess reactive oxygen and nitrogen species. In vitro, the 200 nm nanoparticles were proven to be effective as an antioxidant-based therapy for neurodegenerative disorders and brain damage [66].

CARBON NANOTUBES:

Carbon nanotubes are a form of nanomaterial composed of sheets made of graphite that have been rolled into nanoscale tubes. Carbon nanotubes with open ends or fullerene caps, both single-walled and multi-walled, are available. They can change their physical and biological qualities by functionalizing them with certain chemical compounds, they've recently generated a lot of interest as nanocarrier systems. Carbon nanotubes can also be used to treat cancer by photo thermal activity [67].

Drugs for brain cancer therapy have been delivered utilizing polymer-coated carbon nano dots and chemically functionalized multi-walled carbon nanotubes. The tumor absorption was increased and blood-brain barrier was breached in both in vitro and in vivo investigations [68].

In vitro, using a co-culture paradigm with primary porcine brain endothelial cells and primary rat astrocytes, and in vivo by systemic injection in mice, the penetration of amino-functionalized multi-walled carbon nanotubes through the blood-brain barrier was investigated. The discoveries could pave the way for carbon nanotubes to be employed to deliver medications and biologics to the brain while producing no cell damage [67].

RECENT ADVANCEMENTS IN NANOTECHNOLOGY:

MULTIFUNCTIONAL NANOPARTICLES:

A team of researchers at the University of Michigan been developed a technique to detect and treat the most dangerous types of brain cancer. PEBBLEs are nanoparticles with a diameter of 20 to 200 nanometer that are physiologically localized embedding. The PEBBLES designed by them to carry a multitude of chemicals on their surface, each with its own function. The potential benefit of using these nanoparticles to treat cancer is their multifunctionality. Gadolinium, a common MRI contrast ingredient, was introduced to the PEBBLEs by Kopelman [69].

A large amount of nanoengineering is required for the next functional step. A photocatalyst is carried by each PEBBLE. PEBBLE-based targeted treatments may provide a variety of advantages over standard chemotherapy. PEBBLES are highly targeted to the cancer target, inflict little tissue harm in the surrounding region, and can overcome multidrug resistance (MDR) [69].

A medicine called Photofrin was coupled with iron oxide to make nanoparticles that could be used to target malignant brain tumors. Photodynamic treatment (PDT)' type Photofrin in which drug is injected into the bloodstream and activated by a specific type of laser light to kill tumor cells [68].

OTHER NEW TECHNOLOGIES:

To overcome the barriers of the BBB, a breakthrough technique is used for hitherto worthless drugs to cure CNS diseases. 'LipoBridge' by Genzyme's pharmaceuticals division technology, promises to be a great help to companies developing novel CNS treatments, allowing medicinal chemicals that were previously unable to penetrate the famous blood-brain barrier to do so. As they are larger than 500 Daltons, the BBB will not allow larger molecules to pass, rejects around 95 percent of all viable CNS drugs because [68].

Researchers have also devised a novel method of delivering medications to mice's brains, which has the potential to change the future for people suffering from brain diseases like Alzheimer's.

The new study uses CORVUS, a modified peptide, to deliver tiny mice's brains were injected with interfering RNA (siRNA) molecules with severe brain inflammation [69].

Nanoparticles have been developed by a German organization (NanoDel) to deliver the drugs to brain, retina & spinal cord. A medication bonded with coated surfactant polybutyl-cyanoacrylate nanoparticles which carry drug across the BBB [69].

FUTURE PERSPECTIVES:

When it comes to creating medication systems to treat brain problems, thinking outside the box is essential. The existence of the blood-brain barrier, which protects the brain from outside substances, makes drug targeting and delivery to the brain problematic. To make advances in the successful treatment of common diseases such as brain cancer, neurodegenerative illness, and stroke, novel approaches for greater BBB transit must be created.

Countries are competing to develop and patent Nanotechnology on a global scale. Nanotechnology research is being pursued by several companies around the world, with several billion dollars set aside for it over the next five years. Brain tumor and other diseases of the CNS and other parts of the brain are a major source of concern right now, and the number of cases is rapidly increasing. In order to treat these disorders effectively, an effective brain delivery carrier system is required. To have a deeper understanding, more study is required and mediate crossing mechanisms of BBB and to improve the efficacy of brain delivery methods based on nanotechnology.

Table 1: A complete dataset on biomedical sciences

CNS illnesses that are mostly resistant to smaller compound therapeutic treatment	Smaller compound medication treatment to treat CNS diseases.
Inflammatory illnesses (Multiple sclerosis, Amyotrophic lateral sclerosis, Neuro-HIV, Cancer of Brain or injury of spinal cord, Amyotrophic lateral sclerosis), Stroke or Brain attack, Neurodegenerative disorders.	Chronic discomfort Depression Psychosis Seizure

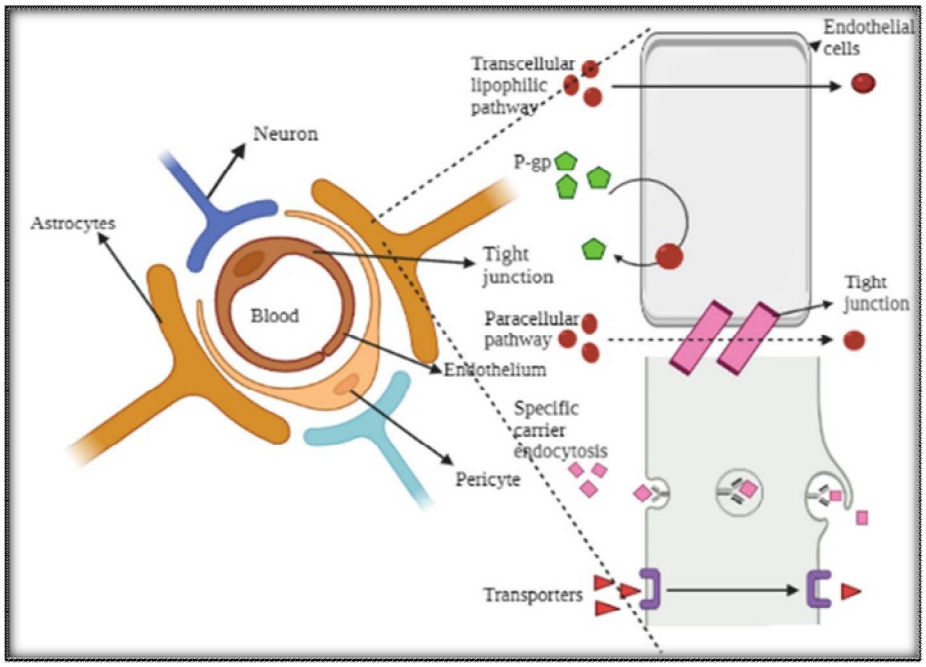

Figure 1: Schematic Diagram of the BBB and transit across it

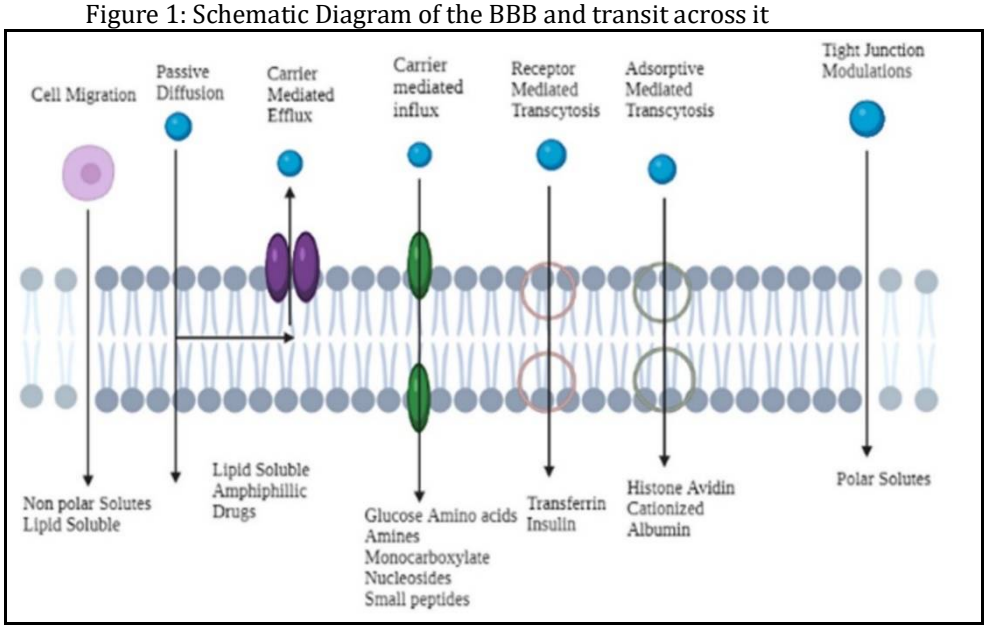

Figure 2: Crossing Blood-Brain Barrier: Transport Routes

CONCLUSION

According to this review, when a surface of colloidal systems is modified properly, before reaching the surface of brain microvascular endothelial cells, may readily penetrate brain capillaries. These modification of surface colloidal particles improve BBB exposure, which increases contact and penetration into brain endothelial cells, due to the prolonged blood circulation. For the treatment of brain disorders, Colloidal carriers effective when medicine is loaded as they provide benefits such as enhanced patient quality of life, reduced drug dose, increased drug viability, non-invasive delivery pathways, less side effects.

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