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The Investigation: Attention on Advanced Therapy of Brain Tumor and Cancer

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ABSTRACT

This is a severe cancer caused by the uncontrolled growth of brain cells within the skull. Tumor cells are notoriously difficult to classify due to their heterogeneity. Main obstacle in the treatment of GBM is the transport of drugs across the BBB. Albumin is a verselet biomaterial for synthesizing nanoparticles. The efficiency of albumin-based delivery systems is determined by the ability to improve tumor targeting and accumulation. Liposomes are effective nano carriers that encapsulate chemotherapeutic drugs to targeted delivery across the BBB. Liposome delivery to the brain consists on binding over the liposomes' surface a biologically active ligand (peptides, antibodies or small molecules) with receptors on the surface of BBB.They are effective nanocarriers that encapsulate chemotherapeutic drugs and facilitate targeted delivery across the BBB. Blocking binding, neutralizing ligand-receptor interaction, internalizing/degrading the target molecule. High-energy radiation, x-rays, gamma rays, and neutrons, are used to kill cancer cells and shrink tumors. This T cells already present near the tumor. Although there is a "proven track record" for identifying cancer cells. The LITT is a minimally invasive surgical procedure in which a laser fiber catheter is placed stereo toxically within the tumor mass with its tip. The PCNA protein is crucial for DNA replication and repair of all growing tumors in nanotechnology and have led to a variety of (NPs) as drug carriers that cross the BBB through 4,444 different strategies. Nano vehicles have great potential and versatility. Nano carriers and lipid-based Nano vehicles have organized in the delivery and promotion of internalization of chemotherapeutic.

❖ **BRAIN CANCER: -**

INTRODUCTION: - Cerebrum tumor (BTs) are abnormal growth of brain tumor cells. uncontrolled and incorrect cell division usually causes brain tumors. the two most important classifications of tumors: -

1. Primary brain tumors develop from cells that are already present in the brain. there are divided into two categories: benign(healthy) and malignant(unhealthy). benign tumors are easily removed and rarely recur. and unhealthy tumor is a fast-growing cancer that spreads to other areas of the brain and spine.

2. secondary brain tumors develop from cancer cells that have spread from other areas of the body. Malignant brain tumors are dangerous because they grow rapidly and can spread to adjacent tissues. Cancer characterized by the uncontrolled growth of cells in the body due to genetic mutations is one of the most common brain tumors today. Cancer tumor diseases around the world. Over the past 4,444 to 2,700 years, medical research has made great strides in understanding and treating this disease. cancer cells typically grow and proliferate rapidly, producing progeny cells with mutated gene. these altered cells resemble the original cells, but the mutations cause them to proliferate more rapidly, a condition known as hyperplasia. Over time, these cells mutate further mutations and develop an abnormal shape called dysplasia. Two types of genes are involved in tumorigenesis: oncogenes and tumor suppressor genes. Brain and centralnervous system 4,444 new ‘’CNS’’ tumors were reported in 308,162 patients, bringing the reported mortality worldwide to 251,329 in 4,44 Brain and CNS cancers cause malignant disease of the brain, cranial nerves, spinal nerves, spinal cord, and meninges. there are over 130 different types and classifications of brain tumors. Brain tumors occur most frequently in children and the elderly. Non-invasive techniques include physical examination of the body and his brain imaging techniques. comparison to a brain biopsy, other imaging techniques, such as CT scans and MRI images are faster andsafer. 4,444 Radiologists use these imaging techniques to detect brain problems, assessdisorder progression, and plan surgeries.

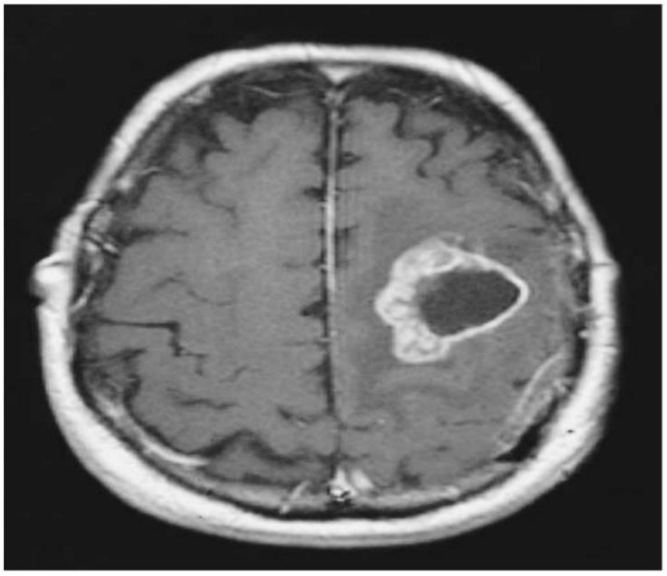


Fig.1: -MRI Of Glioblastoma Multiforme In the Left Frontal Lope Obtained After the Administration of Gadolinium the Irregular Enhancing Margin with Central Necrosis Is Characteristic of The Tumor.

At least three parts of the brain are the brainstem, the cerebrum, and the Cerebellum. A cerebellum is his second largest part of the brain and controls the body's motor activities such as balance, posture, gait, and general movement coordination. The brainstem is connected to the spinal cord. It is located at the base of the brain. All important bodily processes are under the control of the brainstem, including motor, sensory, cardiac, memory, and reflex processes. Its three structural components are the medulla oblongata, pons, and midbrain.

Types of brain tumor: - The World Health Organization (WHO) classifies brain tumors into 120 types. This classification is based on the origin and behavior of the cells, ranging from less aggressive to more aggressive. Specific tumor types are also evaluated, with grade I being the least aggressive (meningiomas, pituitary tumors, etc.) and grade IV being the most aggressive.

Table 1. Types of brain tumors.

Types of Tumors Based on	Type	Comment
Nature	Benign	Less aggressive and grows slowly
	Malignant	Life-threatening and rapidly expanding
Origin	Primary tumor	Originates in the brain directly
	Secondary tumor	This tumor develops in another area of the body like lung and breast before migrating to the brain
Grading	Grade I	Basically, regular in shape, and they develop slowly
	Grade II	Appear strange to the view and grow more slowly
	Grade III	These tumors grow more quickly than grade II cancers
	Grade IV	Reproduced with greater rate
Progression stage	Stage 0	Malignant but do not invade neighboring cells
	Stage 1	Malignant and quickly spreading
	Stage 2	
	Stage 3	
	Stage 4	The malignancy invades every part of the body

The most common type of brain tumor in adults is glioma, which can be divided into HGG and LGG. The WHO further classified LGG as a grade I-II tumor and HGG as a grade III-IV tumor. Detecting brain abnormalities require the use of multiple medical imaging Technologies such as CT, MRI, SPECT, positron emission tomography (PET), (FMRI), and ultrasound (US) can locate brain tumors based on their size, location, shape, and other characteristics. used to identify. The main types of chemotherapy drugs are traditional approaches that often do not eliminate tumor cells, and chemotherapy drugs face the challenge of circumventing both Blood brain barrier and brain tumors (BTB).

BLOOD-BRAIN BARRIER: -

BBB strictly restricts the entry of ions, macromolecules, and nutrients into the brain to protect the brain from potentially harmful substances such as toxins, pathogens, and drugs in the systemic circulation. controlling anatomical and biochemical barriers. These include brain capillary endothelial cells (ECs), pericytes, and astrocyte glial cells, which organize a complexintracellular and intercellular barrier network. The peripheral microvessels of the BBB, the ECs, are characterized by few fenestrations and pinocytic vesicles and are closely connected to tight junctions (zonula occludens), which act as a physical barrier and prevent blood flow. allows unrestricted diffusion of substances from the Cerebrum Claudins, and junctional adhesion molecules (JAM-A, -B, and -C) are among the most abundant proteins that form the zonula occludens complex that restricts paracellular transport. Molecules that cannot easily diffuse through the lipid bilayer, such as small hydrophilic drugs and therapeutic macromolecules including antibodies and antibody-drug conjugates, are typically unable to accumulate in large quantities due to this physical barrier. It is the world's biggest challenge.

The first goal in this field of brain delivery is to find efficient brain delivery vectors that take advantage of physiological pathway mechanisms that disrupt the blood-brain barrier. This vector can be, for example, in the form of peptides, proteins, antibodies, or other specific formulations that target specific receptors of the blood-brain barrier and cross the blood-brainbarrier by transcytosis. Transport of substances across the blood-brain barrier involves multiple transport channels for the following PF proteins and peptides to maintain brain homeostasis; plays a role in preventing Diffusion-controlled transport processes (transcellular and paracellular transcytosis, receptor-mediated transcytosis, transporter protein-mediated transcytosis, cell-mediated transcytosis, etc.).

The paracellular space is accessible only to very small molecules that are water-soluble and have a molecular weight of less than 500 Da. Transcellular diffusion is the process by which dissolved molecules pass through endothelial cells. Through this pathway, the BBB is transported only by a

limited number of selected small chemicals that are non-ionizable, highly hydrophilic, and have the necessary lipophilicity.

Brain barriers exist between cerebral blood vessels and brain parenchyma: - There are three barriers between cerebral blood vessels and brain parenchyma: 1) blood-brain barrier (BBB); 2) blood-cerebrospinal fluid barrier (BCSFB)), 3) Brain fluid barrier (CBB). This BBB is formed by capillary endothelial cells in the brain parenchyma, which separates blood from cerebrospinal interstitial fluid and limits the entry of hydrophilic drugs and high molecular weight neuroactive substances into the brain. A blood-brain barrier essentially consists of brain endothelial cells, astrocytes, pericytes, neurons, and basement membrane (BM). form the neurovascular unit (NVU). The BCSFB is located in the choroid plexus (CP) of the ventricles. CP is an epithelial convoluted structure consisting of a highly vascularized stroma with connective tissue and epithelial cells. The CBB is composed of pin mother cells and astrocytes, exhibits selective permeable and plays a role in the entry of substances within the CSF into the brain parenchyma.

BBB Mechanisms: – Four main mechanisms of molecules to cross the BBB. They can be divided into passive transport (diffusion) and active transport (carrier-mediator transport, endocytosis and cell-mediated transport). Passive transport occurs along the concentration gradient and is independent of ATP energy, whereas active transport requires ATP hydrolysis and proceeds against the concentration gradient.

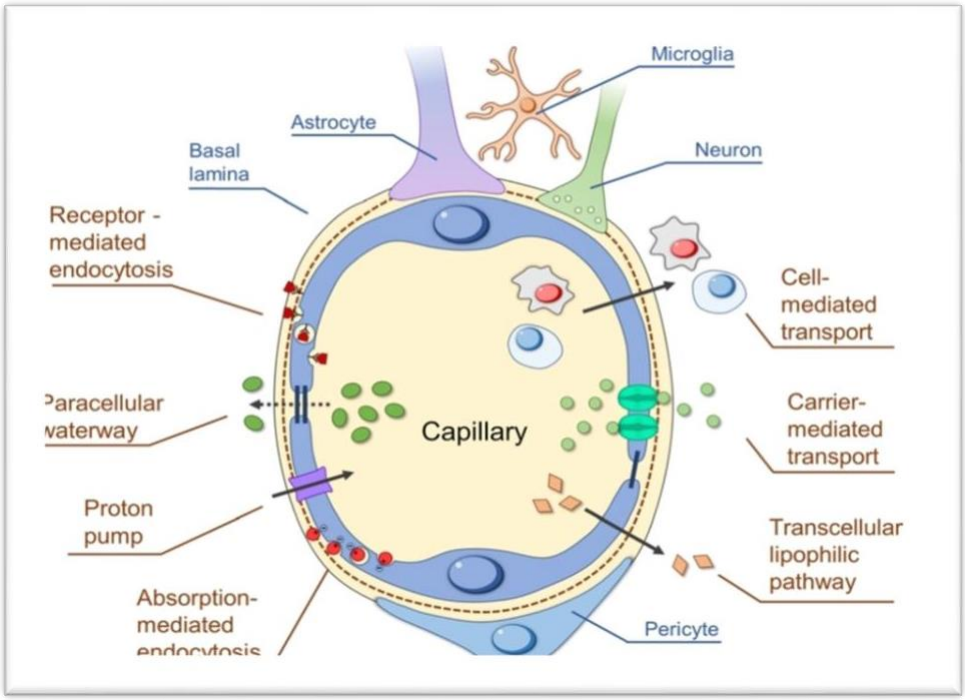


Fig.2.mechanism of transport to the BBB. Diffusion (transcellular lipophilic pathway) carrier mediated transport (CMT), receptor mediated endocytosis (RME), absorption mediated endocytosis (AME), proton pump cell mediated transport and paracellular waterway.

Interface Process: - Lipid solubility and size determine the distribution of substances from blood to CSF and brain tissue, and this method of entry is mainly due to passive diffusion (paracellular transport and transcellular diffusion) and It take place via active transport (solute carrier transport, receptor-mediated transcytosis transport, adsorptive transcytosis transport and vesicles).

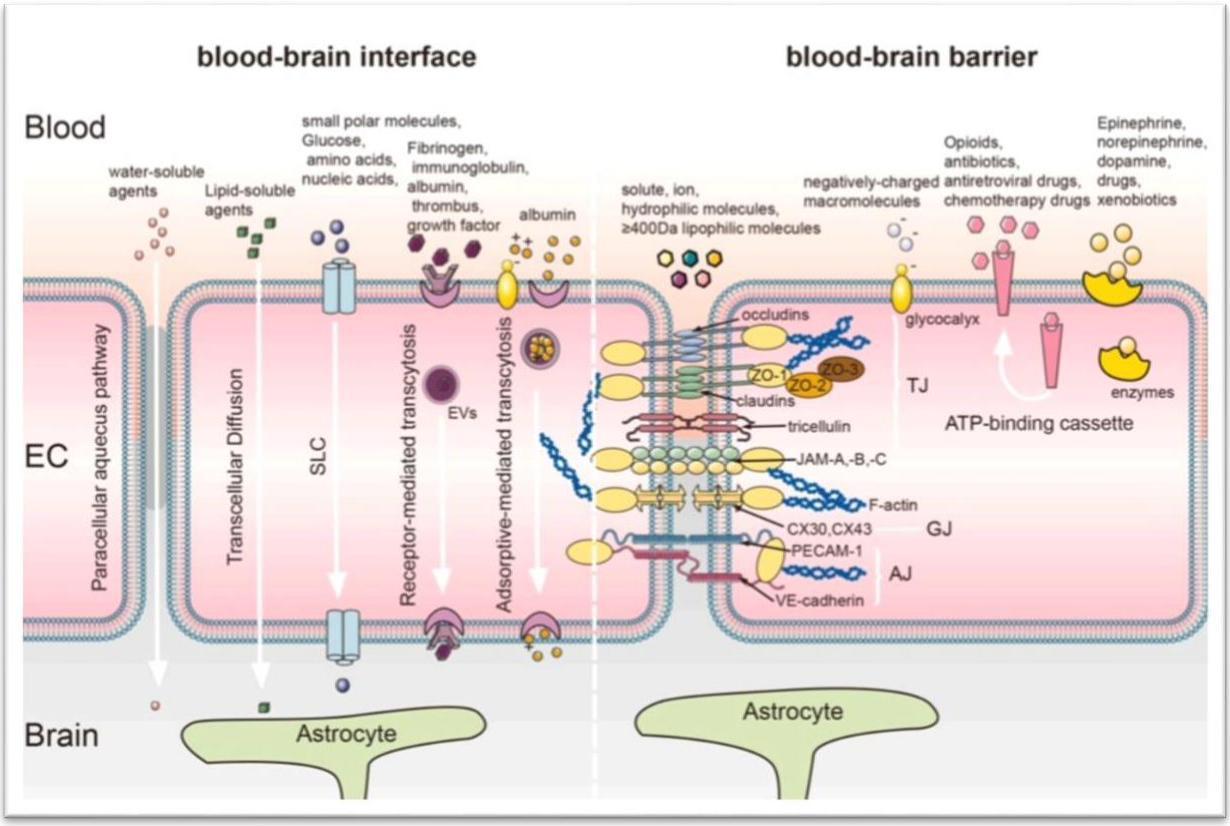


Fig.3 the blood-cerebrum interface and barrier. The blood-cerebrum interface including paracellular transport, transcellular diffusion, solute carrier transport, receptor-mediator transcytosis transport, and adsorptive mediated transcytosis transport. Barrier function is the main function of the BBB, preventing most substance from entering the brain tissue from blood vessels and excreting brain tissue metabolites and the pathways include TJs between brain endothelial cells, and influx.

Dispersing: -

diffusion which allows the transport of substances across cell membranes, can be classified into passive diffusion and facilitated diffusion. Passive diffusion is a process across the BBB caused by a concentration gradient of bioactive compounds between the blood and the extracellular fluid of the brain. Passive diffusion refers to the high lipophilicity of a substance. This allows inorganic molecules such as O2, CO2, and H2O to quickly cross the blood-brain barrier. Facilitated diffusion is the movement of substances through biological membranes, mediated by specific carrier proteins, responsible for the transport of specific molecules or groups of related molecules. Even with facilitated diffusion, mass transport occurs following a concentration gradient, and the rate of this process is significantly faster than passive diffusion. Most essential nutrients such as amino acids, neurotransmitters, hormones, small peptides, and small lipophilic molecules and therapeutic agents

enter the brain by facilitated diffusion. This process involves proton pumps and paracellular water pathways. With the help of proton pumps, protons cross the blood-brain barrier, and the paracellular aqueous pathway is responsible for transporting water-soluble substances into the epithelium by passing through the intercellular spaces between cells.

Pinocytosis: -

Endocytosis is a multistep process in which bioactive compounds enter cells through membrane invaginations. Endocytosis regulates the interaction of cells with their microenvironment. Endocytosis is an energy-dependent transport mechanism that can be divided into three categories, including (i) pinocytosis, (ii) phagocytosis, and (iii) mediated endocytosis. Endocytosis has several steps. The first step is membranous intussusception, during which bioactive compounds are absorbed. Second, the cell membrane forms membrane-bound toward vesicles (called endosomes) that contain bioactive compounds inside. The formed endosomes then transport bioactive compounds through intracellular compartments to organelles. Finally, bioactive compounds are released into the cytoplasm through endosome disruption. The cell membranes of the brain endothelium are negatively charged under physiological conditions. This allows positively charged molecules to interact with negatively charged endothelial cells via electrostatic interactions, promoting the AME mechanism. Positively charged molecules, such as cationic proteins and positively charged polymers (PEI, chitosan), can cross the BBB via the AME. Surface modification of drug delivery systems with such molecules allows them to cross the blood-brain barrier and enter the brain via the AME.

Cell-mediator Movement: -

Cell-Mediated Transport Macrophages, neutrophils and monocytes can participate in cell- mediated transport due to their high mobility. They can migrate across impermeable barriers and release drug cargo at the site of infection or tissue damage. Their migratory properties are used to transport bioactive substances to brain tumors. These cells act as "Trojan horses" to ensure the transport of therapeutic agents across the blood-brain barrier. Cell-mediated transport has serious consequences. Disadvantages such as early drug release, unavailable target delivery and poor drug loading capacity.

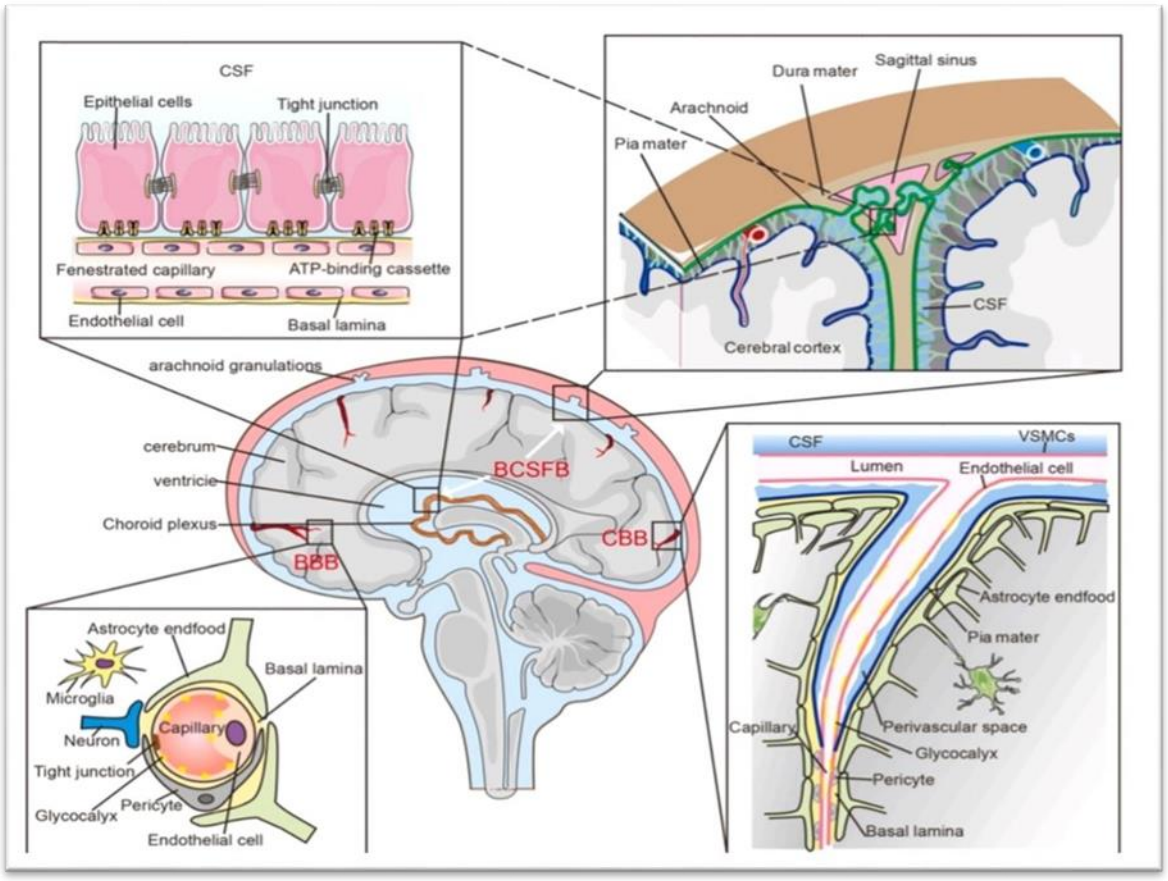
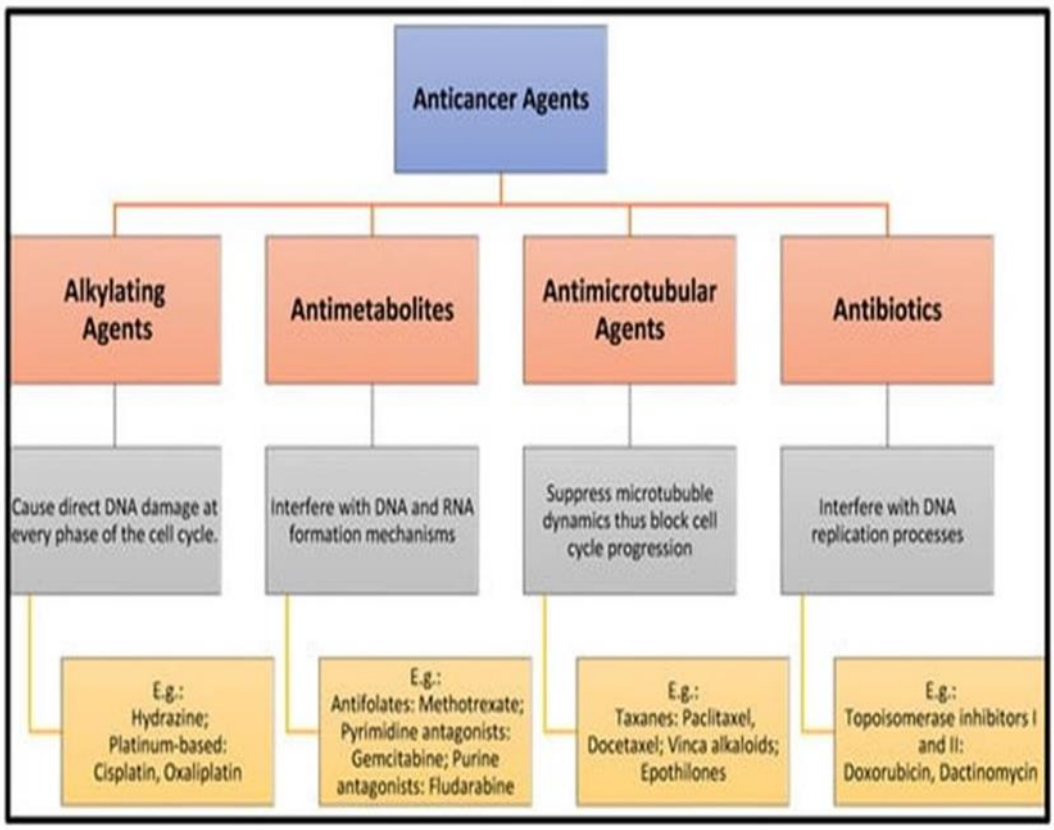


Fig 4: - the brain barrier consists of BBB, BCSFB and CBB.

The classification of drugs to pass the Blood brain barrier.

Table 2- major classes of chemotherapeutic drug.



DRUG DELIVERY SYSTEMS FOR BRAIN TUMOR: - Drug delivery to the brain is improved by using lipid nanoparticles. These nanoparticles extend the residence time of the drug in the blood in brain capillaries and induce a constant concentration of drug from the blood to the brain tissue. This aids the BBB by opening tight junctions (TJs) and taking advantage of the cytopempsis of drug-loaded lipid nanoparticles across the endothelial layer. Lipid nanoparticles with positive surface charges can promote drug accumulation in the brain. The main drawback of using lipid nanoparticles for brain delivery is that lipid nanoparticles are recognized by the reticuloendothelial system "RES". Cells that rapidly remove drug-loaded SLNs from the systemic circulation. Albumin -based nanoparticles that can address the limitations of SNL. Serum albumin, a globular protein secreted by the body. Albumin is non-toxic and non-immunogenic, ensuring excellent biocompatibility with nanoparticles and high stability in water and dilute saline Since the half-life of albumin in the bloodstream is 19 days, drug encapsulated in albumin-based nanoparticles have a lower blood flow than free drugs due to their role in the body (interacting with albumin).

A CLASS OF NANOPARTICLES HAS BEEN STUDIED AS A DRUG DELIVERY SYSTEM FOR BRAIN TUMOR: - Several classes of NPs have been targeted for the development of CNS-targeted drug delivery systems. Many paradigms can be applied to different NP categories. Synthetic NPs (Figure 5) and biological NPs form two major categories of NPs. The former is characterized by a high degree of control over relevant physicochemical properties such as size and surface charge, and includes, among others, lipid-base NPs, polymeric NPs, and inorganic NPs. The BBB posed insurmountable delivery challenges for nanocarriers. These are administered systemically by intravenous injection. To assess whether systemically delivered SPNPs can harbor brain tumors.

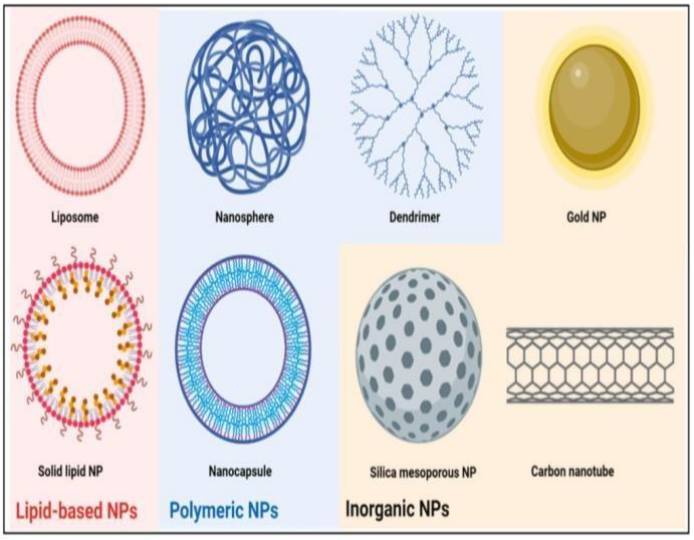


Figure 5. The common structure of the most common synthetic nanoparticles (NPs) used for drug transport.

Lipid-based nanoparticle: -

The two main lipid-based NPs are liposomes and solid lipid NPs (SLNs). Liposomes are spherical vesicles consisting of at least one phospholipid bilayer around an aqueous core and typically range in size from 30 to 2500 nm. Although several liposomal drug formulations have been approved by the FDA as systemic drug delivery systems, none are currently in clinical use for the treatment of brain tumors. Solid lipid NPs (SLNs) are another common subgroup of lipid-based NPs. They differ from liposomes in that they are composed of a phospholipid monolayer surrounding a lipophilic core matrix. Within this core, micellar structures may form around the hydrophilic cargo. SLNs are mainly used as drug delivery systems for nucleic acids. In addition to liposomes and SLNs, Nano Emulsions are also believed to improve drug delivery to CNS tumors. Solid lipid NPs (SLNs) are another common subgroup of lipid-based NPs. They differ from liposomes in that they are composed of a

phospholipid monolayer surrounding a lipophilic core matrix. Drug delivery to the brain can be improved by the use of lipid nanoparticles. These nanoparticles can extend the residence time of the drug in the blood of brain capillaries, resulting in a constant concentration of the medicament from the blood to the brain tissue. This helps overcome the BBB by opening tight junctions (TJs) and exploiting transcytosis of drug-loaded lipid nanoparticles across the endothelial layer. Serum albumin, a globular protein secreted by the body, has several benefits that have attracted the attention of researchers. Albumin is non-toxic, and Nano-immunogenic, ensures excellent biocompatibility with nanoparticles, and exhibits high stability in water and dilute saline. Since the half-life of albumin in the bloodstream is 19 days, drugs encapsulated in albumin-based nanoparticles have a lower blood flow than free drugs due to their role in the body (interacting with albumin). It can stay inside for a long time. Lipophilic molecules such as hormones, fatty acids, vitamins (C, D, folic acid), minerals (copper, zinc, calcium).

Albumin stabilizes the pH of the blood and is responsible for 80% of the osmolality of the plasma. A significant number of SPNPs appeared to cross the blood-brain barrier and were identified within brain tumors.

Polymeric Nanoparticle: -

Polymeric NPs are a diverse group of synthetic NPs. They are composed of natural or synthetic core polymers that form either solid nanospheres or liposome-like nano capsule in which the core polymer forms a shell around a typically aqueous core. The most commonly used polymers in neuro-oncology research are poly (lactic-glycolic acid) (PLGA), poly (β-amino ester), polystyrene (PS), polyanhydrides, chitosan, and polycaprolactone. Dendrimers are a special type of polymeric NPs that can be distinguished from other polymeric NPs by structural differences. They consist of an initiator core that anchors a variable number of “generations” of branched layers and ends with an outer layer of functionalized surface groups that can host imaging, targeting, or therapeutic moieties. Typically, the size ranges from 1 to 15 nm, increasing by 1 to 2 nm with each generation, but doubling the number of surface groups, allowing a high degree of control over size and surface chemistry. An outline of the tunable functionalities of PLGA polymer NPs is shown in Figure 6.

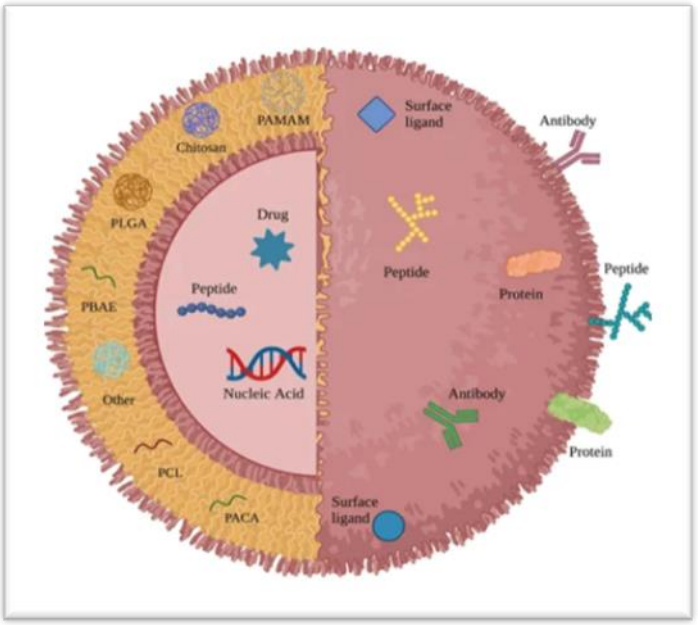


Figure 6. The common structure of a polymeric nanoparticle. PNPs are composed of solid colloids in a matrix and have a wide range of sizes from 1 to 1000 nm. PLGA has a more controllable drug release rate and better encapsulation properties. PBCA is easy to manufacture but has weak drug delivery capabilities. Compared to highly hydrophilic or lipophilic molecules, they biodegrade quickly and are poorly absorb

Inorganic Nanoparticle: - Inorganic NPs are synthesized from inorganic compounds such as gold, silicon dioxide, iron, and carbon and can be fabricated in a variety of sizes and shapes. For example, gold NPs (AuNPs) form nanospheres, nanorods, nanoflowers, nano shell, and nanocages. Carbon forms quantum dots, fullerenes, or nanotubes, and silica is commonly used to fabricate mesoporous NPs (MSNs). Various inorganic NPs possess unique properties, such as photothermal properties of gold and magnetic properties of iron NPs, which lead to other applications such as photothermal radio sensitization therapy and imaging applications, respectively. In particular, carbon nanotubes and mesoporous silica NPs have been investigated as drug delivery systems. The main drawbacks of inorganic NPs are concerns regarding low solubility leading to toxicity and aggregation. Although AuNPs are generally considered safe, MSNs tend to cause hemolysis through interaction with red blood cell plasma.

Biological Nanoparticle: -Biological NPs mainly include Outside cell vehicles (OVs) and cell-based Nano vehicles (CDNs). Outside cell vehicles (OVs) are a group of naturally occurring NPs with a phospholipid bilayer membrane produced by most cells. EVs are classified into three major groups: 4,444 exosomes, macrovesicle, and apoptotic bodies. Exosomes have received the most attention as a

drug delivery mechanism. Extracellular vesicles (EVs) are classified into three groups based on their biogenesis. Micro vesicles are small to medium-size vesicles (100–1000 nm) that arise from the outward budding of the plasma membrane (PM) and contain cytoplasmic proteins. Exosomes are small, uniform vesicles (30–150 nm). that are formed by inward budding of the endosomal membrane, forming intraluminal vesicles (ILVs) within the MVB, and then transported to the plasma membrane where it is released as exosomes. or transported to lysosomes for degradation. Apoptotic bodies are usually large (50–5000 nm), heterogeneously shaped vesicles released by cells undergoing apoptosis. Cell-derived nanovesicles (CDNs) are generated by mechanical extrusion, ultrasound, or freeze-thawing of parent cells. Both EVs and CDNs are composed of phospholipid bilayers that are intrinsically functionalized with different groups of membrane proteins.

Exogenous albumin-binding anticancer drug formulation for cancer treatment: -Development of exogenous albumin-binding anticancer drug formulation. The benefits of albumin have been demonstrated in terms of its pharmacokinetic properties and tumor specificity. Albumin contains many residues such as lysine, aspartate, cysteine, and serine, so drugs can be attached to it through covalent bonds. The amines in albumin can react with drug molecules via N-hydroxy succinimide-activate ester, isocyanate, or aldehyde chemistry, and carboxylic acid or -hydroxyl groups can also be used for drug attachment. It is difficult to control the specific MTX binding sites within the albumin structure, and MTX is rarely released unless albumin is degraded. Gene fusion is a practical approach for conjugating protein/peptide-based drugs to albumin and has been widely used in a large number of 4,444 research papers. Albumin-binding protein Among pharmaceuticals, albumin conjugated to antibodies is often used in cancer treatment. Techniques for forming albumin nanoparticles have advantages and disadvantages and should be carefully selected depending on the desired particle properties and the type of drug to be loaded.

Resolution by C. Weber et: - This is one of the most widely used methods for the formation of albumin nanoparticles. Method using differences in albumin solubility in water and ethanol. When ethanol is added dropwise to an aqueous albumin solution while stirring albumin gradually precipitates as nanoparticles because its solubility in the cosolvent decreases. The precipitated nanoparticles are chemically cross-linked for further stabilization using bifunctional aldehyde linkers, amination between albumin residues, or disulfide exchange reactions. The dissolution method enables the production of highly stable albumin nanoparticles whose size can be freely adjusted according to changes in pH value and temperature. However, during this particle formation process, albumin is denatured by the addition of ethanol and changes in pH and temperature.

Emulsification method: -utilize phase separation of oil and water. When an aqueous albumin solution is poured into an excess amount of oil phase, such as cottonseed oil or castor oil, and stirred rapidly, droplets of albumin solution are formed. After heating the emulsion to evaporate the water, the albumin nanoparticles dispersed in the oil phase are chemically cross-linked, mixed with an organic solvent such as ether or cyclohexane, and centrifuged to remove the viscous oil. Same as the dissoluteness method.

NAB technological: - it was developed by American Bioscience; Inc. Hydrophobic active ingredients are encapsulated in albumin nanoparticles. This technology is known for its method of manufacturing Abraxane (paclitaxel albumin nanoparticles), the only albumin-bound paclitaxel nano formulation approved by the FDA. The organic solution of the hydrophobic active ingredient and the aqueous albumin solution are mixed to form a complex, and the mixture is homogenized under high pressure. The tertiary structure of drug-bound albumin is partially folded by mechanical shear stress, and the unfolded albumin aggregates into nanocrystals through electrostatic and hydrophobic interactions. NAB technology not only offers high productivity but also anti-cancer benefits.

Spray dry: - it is an industrial method for producing ultrafine powder formulations for nasal and pulmonary drug delivery. Formation of albumin nanoparticles by nano spray drying involves co dissolving albumin and drug and spraying the solution through a small diameter nozzle to generate a nanosized aerosol. The albumin solution aerosol is dried under reduced pressure by heating, and the resulting nano powder is collected using an electrostatic precipitator. Nano spray drying is a promising technique for producing albumin nanoparticles.

A variety of inorganic nanoparticles can be used to develop albumin nanoparticles. Nanoscale inorganic materials such as gold and iron oxides are highly unstable under normal conditions and pose a potential toxicity hazard. Albumin formulation of iron oxide nanoparticles improved colloidal stability and biocompatibility for magnetic thermotherapy.

The ability of albumin to attack cancer cells: - vascular hyperpermeability and impaired lymphatic drainage, a well-known EPR effect in solid tumors, are proposed as mechanisms responsible for the passive targeting of many nanocarriers in solid tumors. has been done. A key feature of the EPR effect is the highly permeable tumor vasculature, which increases the permeability of particles between 20 and 200 nm in size. Because tumors lack lymphatic vessels, HSA can leak extravasally and accumulate in the interstitial space of the tumor. The main role of EPR effect as a mechanism responsible for passive targeting of delivery nano system in solid tumors. Albumin can specifically bind to glycoprotein 60 (gp60) and SPARC, thus actively increasing the uptake of nanoparticles. This

unique absorption mechanism allows albumin-based nanoparticles to overcome drug efflux mechanisms in tumor cells.

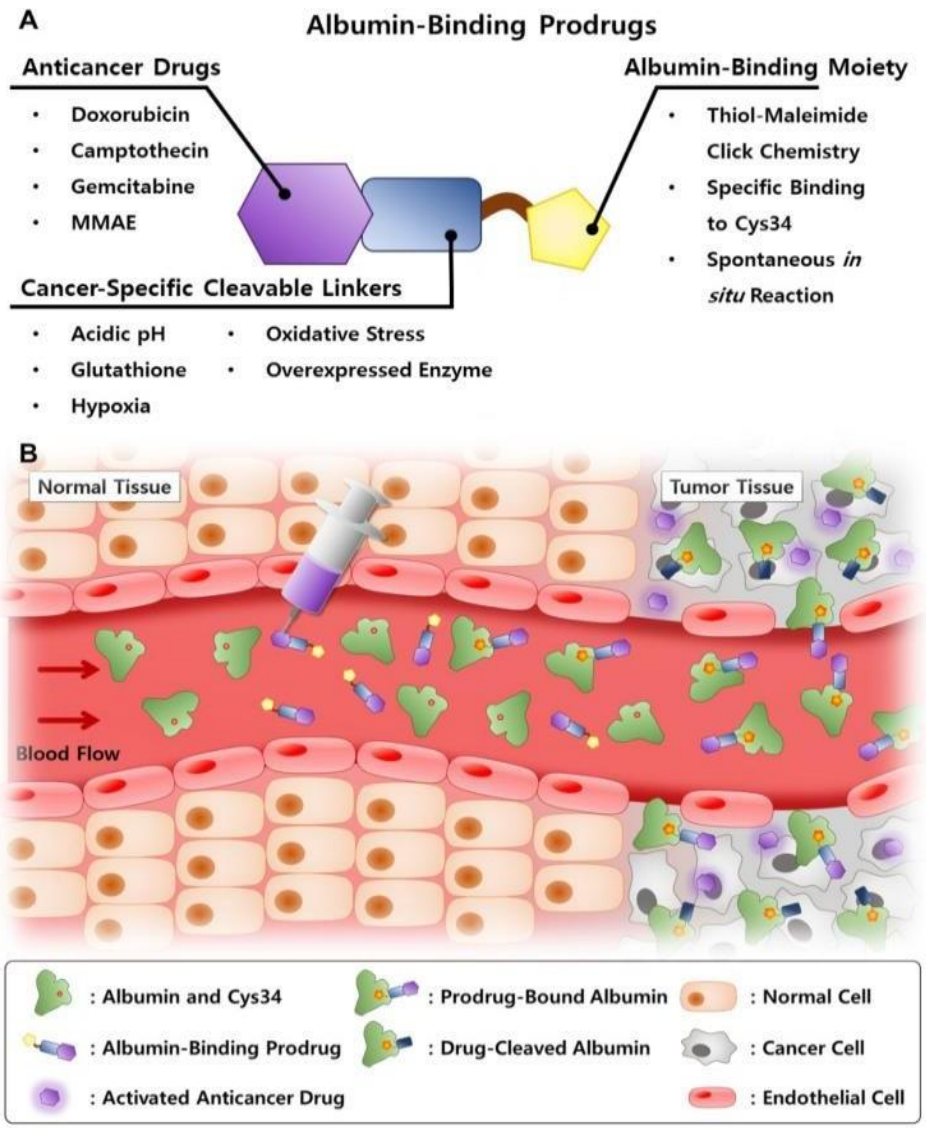
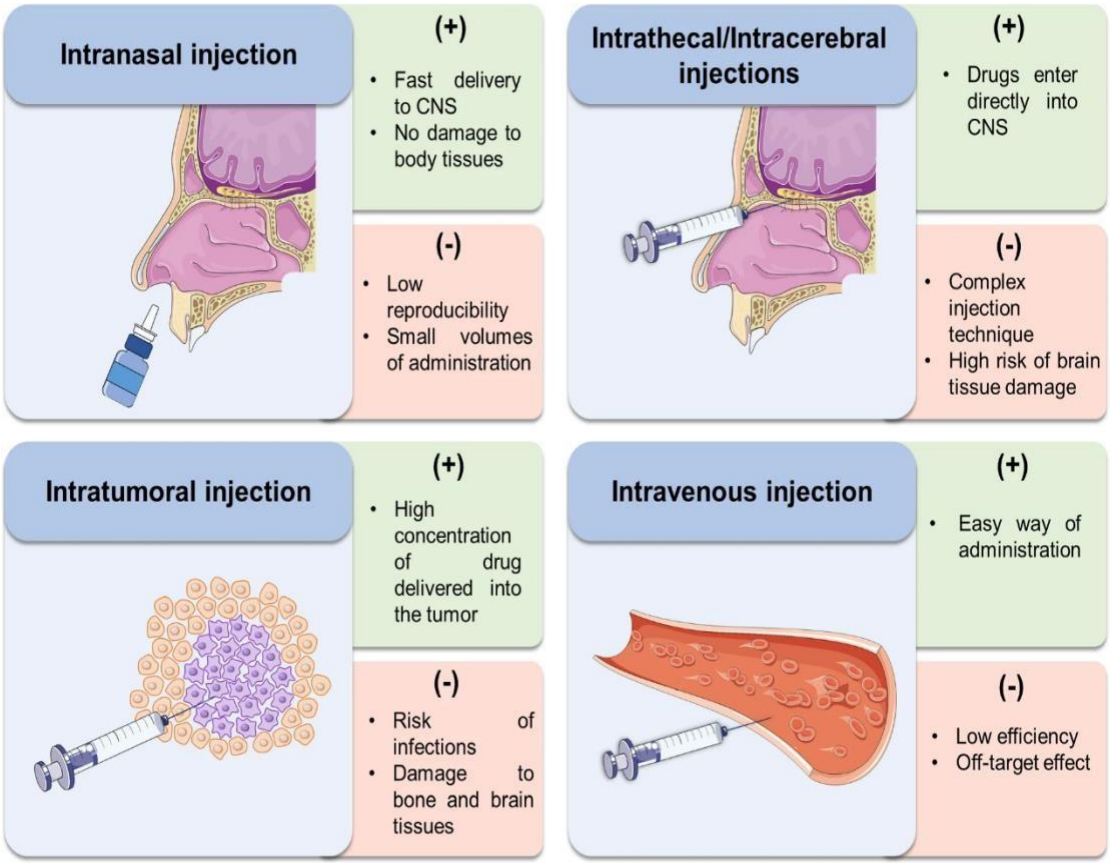


Fig 7. (**A**) Structure of the albumin-binding prodrug and explanations about each constituent.

1. Schematic illustration of the mechanism of action of albumin-binding prodrug.

It can stay inside for a long time. Lipophilic molecules such as hormones, fatty acids, vitamins (C, D, folic acid), and mineral (copper, zinc, calcium). Albumin stabilizes the pH of the blood and is responsible for 80% of the osmolality of the plasma. These methods can be classified into two types: (1) invasive approaches and (2) non-invasive approaches. Invasive methods of drug administration include intraventricular (ICV), intrathecal, intracerebral, and intra-tumor injections. transporters and metabolic enzymes.



Fg.8. Schematic representation of intranasal, intrathecal/intracerebral, intra tumoral and intravenous injections for the delivery of therapeutic molecules to the brain tumor

Intrathecal and Intracerebral Injection: -Intrathecal techniques involve injecting the drug directly into the epidural or subarachnoid space. Molecules injected intrathecally diffuse through the meningeal layers and enter the cerebrospinal fluid. Therefore, such drug administration is expected to be more effective than intravenous injection. Many potential nanocarriers have been investigated for intrathecal delivery: e.g. alginate/chitosan complex and maltosyl-beta-cyclodextrin to improve the delivery efficiency of bupivacaine. Direct injection into the brain shows good results in treating brain tumors.

Intra tumoral Inoculation: - Intra tumoral Injection A method of administering therapeutic drugs to brain tumors. Local drug delivery aims to increase drug concentration at the tumor site and reduce systemic toxicity. For example, liposomal DOX polymer structures have received clinical approval for intracranial treatment of resectable GBM. Direct injection of fluid into tumors is also being studied clinically. This method allows the drug to remain at the tumor site for a long time and act locally. Complex transplantation procedures, risk of infection, local toxicity of the drug, and rapid removal of the drug from the brain parenchyma significantly limit the application of this method.

Intravenous inoculation: - Intravenous injection the drug is administered (so-called arterial chemotherapy). Intravenous administration involves the use of drug delivery systems and is via CMT, RME, and AME (discussed below). Intravenous injection may also result in nonspecific accumulation of the drug in other organs, namely the liver, spleen, and kidneys. This method has several drawbacks, mainly related to the destructive mechanism of drug delivery across the blood-brain barrier.

Intranasal Administration: - Intranasal Administration This is an alternative method of administering therapeutic agents directly into brain tissue. Intranasal delivery of therapeutic agents occurs via the trigeminal and olfactory nerves, and the drugs are transported directly into the cerebrospinal fluid, bypassing the blood-brain barrier. Intranasal administration has several advantages, including simplicity, safety, convenience, and painlessness. The main advantage of intranasal administration is the rapid absorption of the drug within the nasal cavity. Intranasal administration of the nanocarrier formulation at the required dose. Various devices can be used for this purpose. From simple nasal sprays to more complex devices such as electronic nebulizers. The nab-PTX (PTX-encapsulated albumin nanoparticles) has a 9.9-fold increased binding capacity to endothelium and is 4.2-fold more efficient compared to Chromophore EL-PTX (polyhydroxy-based vehicle) is shown. ethylated castor oil incorporating PTX). Albumin can bind to the gp60 receptor, also called albumin, with a molecular weight of 60 kDa. This receptor is present on the surface of vascular endothelial cells and is transported into tumors via interstitial transcytosis. In nanotechnology, many different types of nanomaterials have been investigated as potential carriers due to their unique properties to fight brain tumors. These include small size, high drug loading capacity, simple design, good stability, biocompatibility, and biodegradability. Nano carrier-based delivery of drugs across the BBB without affecting BBB structure or function. The use of Nano vehicles (NVs) to deliver drugs, genes, or other therapeutic agents across the blood-brain barrier. Development and application of tailored delivery Nano vehicles applicable across the BBB (Figure 9). NP-mediated brain drug delivery, the specific features of the BBB, the role of NPs, and the specific environment of NPs are largely unidentified. This raises the unique role played by NPs in drug delivery across the blood-brain barrier, the recent successes and achievements of Nano vehicle-based drug delivery, and the potential of Nano vehicle-based technology to treat brain tumors.

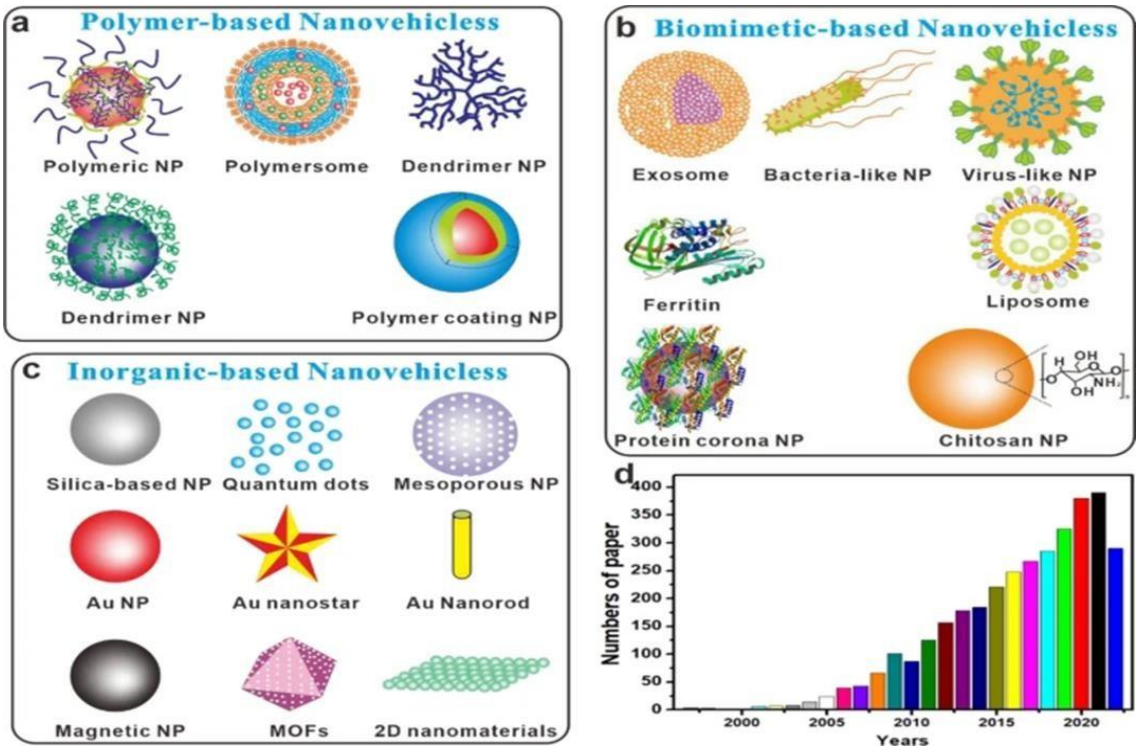


Fig 9: - a, b, and c Schematic and structure of Nano vehicles used to cross the BBB; d Annual frequency.

The Delivery of drugs across the BBB without compromising its structure or functionality, using Nano vehicles (NV) to transport a drug, gene, or other Therapeutic agent over the BBB.

Nano vehicles are spherical lipid bilayer vesicles composed of lipids. Typically, they are classified based on their size, which ranges from 200 nm to 1000 nm. The first class is small unilamellar vesicles (SUVs) with a single bilayer in the size range > 200 nm, followed by large unilamellar vesicles (LUVs) and giant unilamellar vesicles in the size range of 250 -1000 nm. This is followed by the vesicle (GUV). Another class includes multilamellar vesicles (MLVs), which consist of multiple concentric bilayers, and multivesicular vesicles, which have many smaller vesicles encapsulated within a larger vesicle. The surface of these vesicles can be easily functionalized with various ligands and serve as multifunctional Nanocarrier for targeted drug delivery. Polymeric and liposomal nano vehicles for cancer therapy.

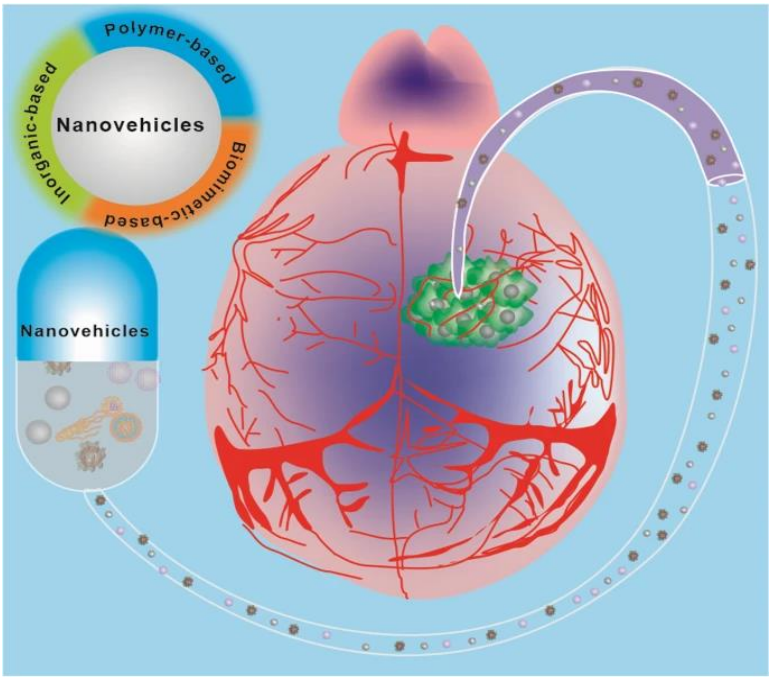


Fig.10. delivery nano-vehicles for precise brain tumor therapy

Nanocarrier and lipid-based Nano vehicles have been organized in the delivery and promotion of internalization of chemotherapeutic/anti-angiogenic drugs, with targeting specificity for both cancer cells and vascular abnormalities. It Provide nano vehicles applicable across the BBB. The role of NPs, and their unique environment. For this reason, we focus on the unique role played by NPs in drug delivery across the blood-brain barrier, the recent successes and achievements of nano vehicle-based drug delivery, and the potential of Nano vehicle-based technologies in future brain therapies. Nanoparticle-based drug carriers should ideally have a large specific surface area and strong interactions with the drug they transport. Nano vehicles have shown great potential and versatility in their ability to simultaneously encapsulate many chemicals within a controlled drug delivery system and direct them to the most inaccessible parts of the brain to inhibit tumor growth. The surface charge of nano vehicles plays opposing roles in bridging the blood-brain barrier, and these roles need to be balanced. Because endothelial cells have complementary negative charges, positively charged cationic nanoparticles are thought to have a higher potential to penetrate the blood-brain barrier (BBB). However, the toxicity and half-life of anionic or neutral NPs are significantly lower than those of cationic nano vehicles. Nano vehicles such as liposomes, polymeric nanoparticles, dendrimers, and inorganic-based nano vehicles provide improved drug stability, enhanced drug penetration across the blood-brain barrier, and targeted drug delivery.

ADVANCES TREATMENT OF BRAIN TUMOR: -

Molecular Targeted Therapy: - The two main types of molecularly targeted therapies are monoclonal antibodies (mAbs) and small molecule kinase inhibitors (SMKIs). mAbs target extracellular ligands (e.g., bevacizumab for vascular endothelial growth factor [VEGF]), membrane receptors (e.g., trastuzumab for HER2 and cetuximab, panitumumab for EGFR), and membrane-associated proteins (e.g., rituximab for CD20). and acts through a ligand. blocking binding, neutralizing ligand-receptor interaction, or internalizing/degrading the target molecule. Advanced molecular profiling and personalized treatment of brain tumors. This could lead to an effective treatment plan based on the patient's tumor characteristics and improve treatment outcomes. Additionally, accurate prognosis helps patients make their own decisions. Imaging techniques such as MRI are often not sufficient to understand the characteristics of each patient's tumor. In this special issue, studies are discussed on the application of stereotactic biopsy of brainstem lesions to molecularly targeted therapy.

Mechanisms of anticancer effects of molecular target treatment: - Molecular target therapy achieves anticancer effects through various mechanisms, include Inhibition of cell proliferation, metastasis, angiogenesis, induction of apoptosis, and reversal of multidrug resistance. Several targeted therapeutic agents, alone or in combination with chemotherapeutic agents, also enhance CD8+ T cell recruitment and natural killer cell cytotoxicity, downregulate immunosuppressive myeloid cells, and inhibit immunogenic cell death. inducing anti-tumor immunity in the host.

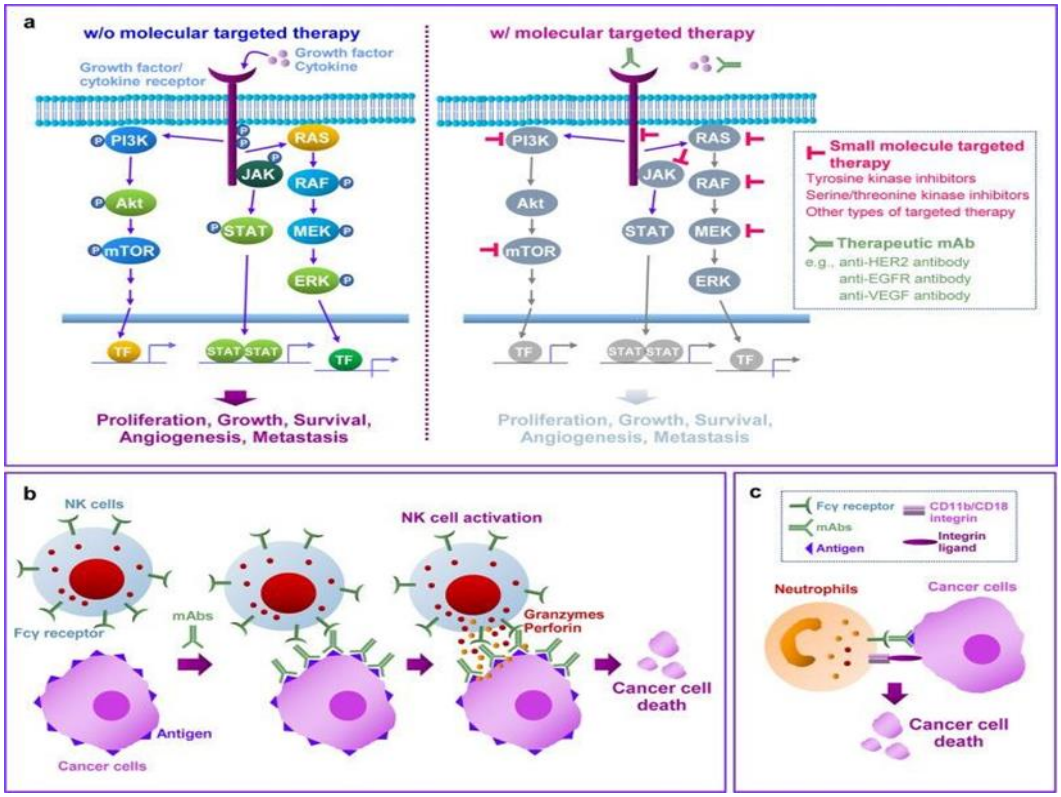


Fig 11: - Schematic diagram of the main protumor signal transduction pathways and their inhibition by molecular targeted therapeutic agents. **b**, **c** Schematic diagrams for antibody-depended cellular cytotoxicity.

Radiotherapy (RT): - it is used as an effective treatment for cancer. High-energy radiation, such as x-rays, gamma rays, and neutrons, can be used to kill cancer cells and shrink tumors. RT in tumor tissues aims to maximize local tumor suppression and minimize side effects on normal tissues. In parallel to the treatment of malignant brain tumors, several treatments such as surgery, radiotherapy, and systemic cancer treatment can be used alone, in combination, or sequentially, depending on the stage, reactive and biological properties. is used clinically in cancer treatment. Comorbidities and the patient's overall functional performance. Systemic cancer treatments include a wide range of anti-cancer drugs aimed at curing, palliating, relieving symptoms and improving quality of life, and also include cytotoxic chemotherapy, hormonal agents, targeted therapies, and anti-tumor immunotherapies. It will be Cytotoxic chemotherapy impairs the survival of actively proliferating cells by interfering with DNA and RNA synthesis, blocking mitosis, and/or forming covalent bonds with DNA, RNA, and proteins inhibits.

Immunotherapy: - The most promising immunotherapeutic approaches for the treatment of

glioblastoma are immune checkpoint inhibition, T cell transfer therapy, vaccination, and oncolytic virus therapy (OVT). These methods utilize the immune system to recognize and specifically attack tumor cells. T-cell transfer therapy or adoptive T-cell therapy is a type of immunotherapy that involves two main approaches. Tumor-infiltrating lymphocyte (TIL) therapy and chimeric antigen receptor (CAR) T-cell therapy. This involves T cells already present near the tumor. Although there is a "proven track record" for identifying cancer cells, the number of cancer cells is too small to overcome immune suppression. CAR T cell therapy introduces synthetic T cell receptors into T cells, giving them the ability to recognize tumor-particular surface antigens and trigger an MHC-independent immune response. Targeted CAR T cells reached the tumor from the peripheral blood, but no meaningful response was detected.

Laser Interstitial Thermotherapy (LITT): - Laser Interstitial Thermotherapy (LITT) is a minimally invasive surgical procedure in which a laser fiber catheter is placed stereo toxicity within the tumor mass with its tip. Non-ionizing laser light is introduced through this catheter to increase the temperature of the target tumor volume and determine the extent of ablation during simultaneous magnetic resonance imaging. The photons heat the target tissue, either directly through absorption or indirectly through scattering into adjacent tissues, causing denaturation of DNA and proteins and cell death. At temperatures above 60 degrees Celsius, cell death becomes irreversible. Between 46 and 60 degrees Celsius, the time a cell takes to die is inversely proportional to the temperature and the time spent at that temperature.

The Town of Hope, one of the largest cancer research and treatment organizations in the United States, states that ``phosphorylation of proliferating cell nuclear antigen (PCNA) is one possible cause of increased nucleic acid replication errors in cancer cells. "Proliferating cell nuclear antigen (PCNA) once considered too demanding for a targeted therapy, and in preclinical study, it has developed a targeted chemotherapy that apparently destroys all solid tumors." The anticancer drug AOH1996, developed over the past 20 years, targets cancerous variants of PCNA. In its mutated form, the PCNA protein is crucial for DNA replication and repair of all growing tumors. AOH1996 is a small molecule PCNA inhibitor used in over 70 cancer cell lines and several normal control cells. They found that AOH1996 selectively kills cancer cells by interfering with the reproductive cycle of normal cells. It targets so-called transcription-replication conflicts, which occur when the machinery responsible for gene expression and genome replication collide. PCNA is a multilayer protein conserved in

eukaryotes that plays an important role in DNA replication and is used as a marker for DNA replication. PCNA is a multilayered protein conserved in eukaryotes that plays an important role in DNA replication and is used as a marker of tumor progression. PCNA is an important anticancer target due to its role in DNA replication/repair. (Chemotherapy drugs exploit this genetic instability by inducing additional DNA damage and overwhelming the cancer cell's repair systems. To combat cancer-associated isoforms of proliferating cell nuclear antigen (caPCNA), which play a central role in DNA replication and damage response networks. Small molecule and peptide drugs that specifically target caPCNA can selectively attack cancer cells without causing significant toxicity to normal cells. (Intrinsic DNA double-strand breaks and transcription-replication competition, a major cause of genomic instability, may have important implications for cancer therapy. Proliferating cell nuclear antigen (PCNA) plays a role in DNA replication and repair. Through a rational approach to drug discovery, we identified the small molecule PCNA inhibitor AOH1996, which selectively kills cancer cells and plays an important role in DNA synthesis and DNA repair. PCNA forms a homotrimeric ring structure surrounding DNA1 and functions as the central “hub” of the replisome.

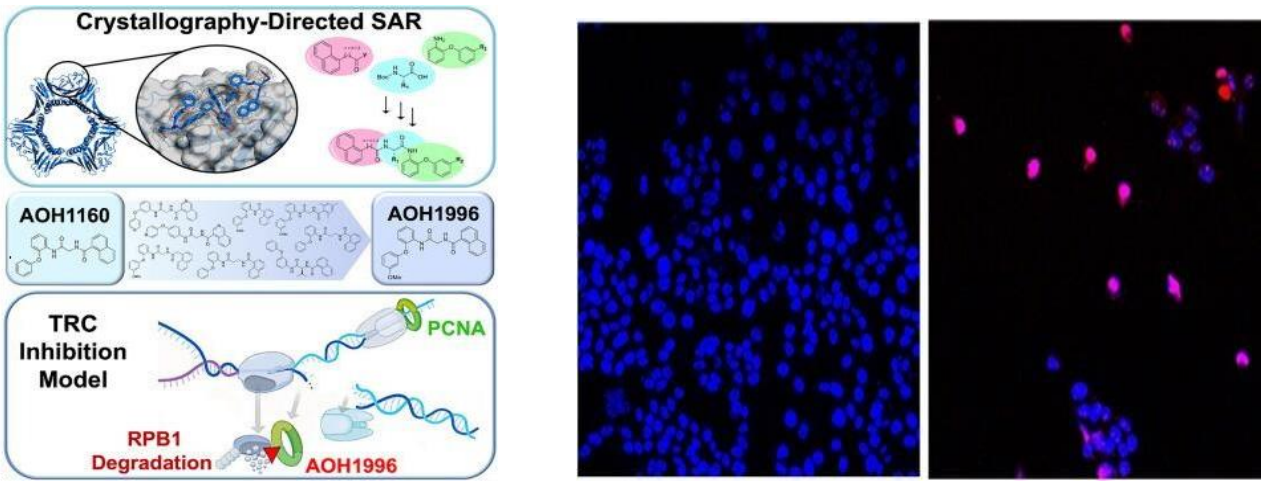


Fig.12: The City of Hope-developed small molecule AOH1996 targets a cancerous variant of the protein PCNA. In its mutated form, PCNA is critical in DNA replication and repair of all expanding tumors. Here we see untreated cancer cells (left) and cancer cells treated with AOH1996 (right) undergoing programmed cell death (violet).

Tested the small molecule PCNA inhibitor AOH1996 in more than 70 cancer cell lines and several normal control cells. They found that AOH1996 selectively kills cancer cells by interfering with the reproductive cycle of normal cells. This targets so-called transcription replication conflicts, which occur when the machinery responsible for gene expression and genome replication collide.

The investigational treatment prevented cells with damaged DNA from dividing in the G2/M phase and making copies of the defective DNA in the s phase. As a result, AOH1996 caused cancer cell death (apoptosis).

Summary: - A brain tumor is an abnormal growth of cells in the brain or surrounding tissue. It is either cancerous (malignant) or non-cancerous (benign). Treatment options for brain tumors include surgery, radiation therapy, and chemotherapy. In this review, we have discussed the general properties of albumin in drug delivery. Furthermore, we also discussed the development process and clinical implementation of exogenous albumin-binding anticancer drug formulations. While some brain tumors can be successfully treated and controlled, others can be more difficult. Delivery of drugs across the blood-brain barrier without affecting the structure or function of the blood-brain barrier by using nano vehicles (NVs) to transport drugs or other therapeutic agents across the blood-brain barrier. Nano vehicles such as liposomes, polymeric nanoparticles, dendrimers, and inorganic-based nano vehicles provide improved drug stability, enhanced drug penetration across the blood-brain barrier, and targeted drug delivery. liposome delivery to the brain consists to binding over the liposomes' surface a biologically active ligand (peptides, antibodies or small molecules) with receptors on the surface of BBB. They are effective nanocarriers that can encapsulate chemotherapeutic drugs and facilitate targeted delivery across the blood–cerebrum barrier (BBB). Polymeric nanoparticles (PNPs) up to be the ideal vehicles for therapeutic delivery to the brain owing to their unique physicochemical characteristics like high biocompatibility, biodegradability, and low toxicity. Dendrimers are a class of well-ordered nanosized hyper-branched polymers. Drug molecules can be attached to the surface groups or encapsulated within the interior void of the dendrimers. Due to the presence of a vast number of functional groups on the dendrimer surface, various therapeutic molecules and drugs can be efficiently accommodated by conjugation. Inorganic-based nano vehicles. Inorganic nanoparticles have benefits over polymeric and biomimetic nanoparticles when it comes to medication delivery

in the brain because of their size-dependent, different material, and great stability physicochemical features.

CONCLUSION: -

Learn about types of brain tumors and their treatments. Applications of albumin-based drug delivery systems from the past to the present. and to research advanced treatments for brain tumors. Major advances in improving the effectiveness and safety of treatments. These systems have challenges such as the blood-brain barrier and limited drug penetration. The development of nano vehicles in drug delivery systems for brain tumors has shown more promise in overcoming these limitations. Nano vehicles such as liposomes and polymeric nanoparticles have improved drug penetration across the blood-brain barrier. We also discussed the general properties of albumin in drug-transport systems. Classification and detection of brain tumors in MRI images. MRI detects the presence of tumors and is used to detect brain tumors. liposome delivery to the brain consists on binding over the liposomes' surface a biologically active ligand (peptides, antibodies or small molecules) with receptors on the surface of BBB. They are effective nanocarriers that can encapsulate chemotherapeutic drugs and facilitate targeted delivery across the blood-cerebrum barrier (BBB). blocking binding, neutralizing ligand-receptor interaction, or internalizing/degrading the target molecule. Advanced molecular profiling and personalized treatment of brain tumors. High-energy radiation, such as x-rays, gamma rays, and neutrons, can be used to kill cancer cells and shrink tumors. This involves T cells already present near the tumor. Although there is a "proven track record" for identifying cancer cells. Laser Interstitial Thermotherapy (LITT) is a minimally invasive surgical procedure in which a laser fiber catheter is placed stereo toxicity within the tumor mass with its tip. In its mutated form, the PCNA protein is crucial for DNA replication and repair of all growing tumors.

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