Volume 9, Issue 4, October 2022 ISSN: 2348-8565 (Online)
International Journal of Modern Engineering and Research Technology
Website: http://www.ijmert.org Email: editor.ijmert@gmail.com

Blood-Brain Barrier

Shilpi Rawat
Assistant Professor
Barkatullah University
Bhopal (M.P.), India
Email: shilpi6feb@gmail.com

Hemlata Bundela Awasthi
Assistant Professor
St. Aloysius Institute of Technology
Jabalpur (M.P.), India
Email: hemlatajbp@gmail.com

ABSTRACT

Blood vessels are critical to deliver oxygen and nutrients to all of the tissues and organs throughout the body. The blood vessels that vascularize the central nervous system (CNS) possess unique properties, termed the blood–brain barrier, which allows these vessels to tightly regulate the movement of ions, molecules, and cells between the blood and the brain. This precise control of Central Nervous System homeostasis allows for proper neuronal function and also protects the neural tissue from toxins and pathogens, and alterations of these barrier properties are an important component of the pathology and progression of different neurological diseases. The physiological barrier is coordinated by a series of physical, transport, and metabolic properties possessed by the endothelial cells (ECs) that form the walls of the blood vessels, and these properties are regulated by interactions with different vascular, immune, and neural cells.

Keywords:— *Blood-Brain Barrier, Endothelial cell, Astrocytes, Pericytes, Neuron.*

I. INTRODUCTION

The concept of blood-brain barrier was established almost a century ago. When the pigment is injected into the blood vessels of the animals, it is, of course, affect all of the tissues, but not the brain. The Blood-Brain Barrieris a highly selective, structural and biochemical barrier that allows the brain's nutrition to pass through and protects against environmental and negative external factors. It combined the details of the extrinsic environment with the indications of the intrinsic environment to perform certain tasks. With all the particular tasks that take place at the neuronal level, it is paramount that the chemical environment in which these cells function is strictly controlled. The Blood-Brain Barrier (BBB) is a term familiar with the unique characteristics of the microvascular system of the central nervous system. The central nervous system consists of the brain and spinal cord, two major barriers to the attention of the blood-brain barrier, which is made up of endothelial cells of the brain's microvessels, as well as blood and cerebrospinal fluid barriers in the epithelial layer. The arachnoid matter, includes the choroid plexus, ventricles of the brain, and the external surface of the brain [15]. To maintain normal brain function, the neural environment must be preserved within a narrow homeostatic range; this requires tight regulation of the transportation of cells, molecules, and ions between the blood and the brain. Such tight regulation is maintained by a unique anatomical and physiological barrier, formed collectively in the central nervous system (CNS). The existence of a physical interface between the Central Nervous System and the

peripheral circulation and the vascular capacity was first described by Paul.

The blood-brain barrier is characterized by its distinctive structure, high efficiency, and by way of to the interaction between the cellular and the cellular components. The primary role of the Blood-Brain Barrier is to provide excellent conditions for smooth operation of the neural network [16].In addition, it increase the efficiency of nerve cells by allowing glucose transport [17].

This process allows for the movement of other molecules through the passive diffusion, as well as the selective and efficient transport of various ions, nutrients, macromolecules and organic anions. The only lipid-soluble molecules can freely diffuse through capillary of the endothelial membrane, it can passively cross the Blood-Brain Barrier, which may be said to be unreliable, especially for fat-soluble compounds with polar molecules, and a small ions. But the lipophilicity of itself is not determined by the membrane permeability of the molecule [18]. The **barrier** (Blood-Brain Barrier) **may be a** selective impermeable membrane that controls the passage **of huge and little** molecules into the microenvironment of neurons. Obstacle cells actively transport metabolic products using certain transport proteins. It achieves this with **the assistance** of several cellular transport channels spread along the membrane.

II. Cellular Transport Channels

Preservation of an optimal environment for synaptic and neural function is achieved by specific ion channels and transporters. Water molecules can also cross the Blood-Brain Barrier through ion channels. Due to regulated ionic movement, potassium concentration in the CSF and brain interstitial fluid are maintained at ~2.5–2.9 mM despite the higher concentration of potassium in the plasma (~3.5–5.0 mM). In fact, potassium concentration can vary strongly during body exercise nutrition, or pathological conditions and may increase to levels as high as 10 mM invenous blood. If such an increase in potassium concentrations would occur in the brain, a significant change in neuronal activity, specifically epileptic discharges, would be triggered. The Blood-Brain Barrier thereby protects the nerve cells from such variations. The Blood-Brain Barrier is similarly largely impermeable to most ions such as Ca2+ and Mg2+. pH also is actively regulated at the Blood-Brain Barrier.

- Amino acid transporters
- Glucose transporter
- Nucleouside and nucleotide transporters
- Monocarboxylate transporters
- Ion transporters (Na+/K+-ATPase pumps)

2.0 Essential Features of the Blood-Brain Barrier:

An important feature of the Blood-Brain Barrier is its low and selective permeability to molecules **which may** be attributed to its unique biological characteristics.

Blood-Brain Barrier limits the free exchange of material between blood and brain. It provides essential nutrients to the brain and the production of metabolites from the brain to the blood.

The blood and brain barrier prevents the spread of solute **within the** blood, the passage of germs **and enormous** or hydrophilic molecules entering the **spinal fluid**, while allowing the spread of hydrophobic molecules (O2, CO2, hormones) [19]

Obstetric cells idly transport metabolic products like glucose across the barrier using certain transport proteins .

Obstruction also prevents the passage of immune defenses, like marking of antibodies, immune cells, and molecules, within the Central Nervous System, thus protecting the brain from damage due to immune events .

It delivering essential nutrients to the brain and releasing metabolites from the brain to the bloodstream, removing toxins or unwanted substances from the brain into the bloodstream to prevent brain function,

The regulation of endocrine function. However, in pathophysiological conditions, such as being hit tumor, infection, ischemia, or other factors, Blood-Brain Barrier is sensitive to damage, which leads to increased permeability and loss of barrier function.

It regulating hormonal functions. However, under pathophysiological conditions, such as tumor damage, inflammation, ischemia, or other factors, the Blood-Brain Barrier is at risk of injury, causing an increase in penetration and loss of "barrier" function.

It plays a key role in managing homeostasis in the brain and implements controls that are protected from the entry and production of molecules [20].

2.1 Cells of the Blood-Brain Barrier

a: Endothelial cells:

Endothelial cells (ECs) are mesodermal derived modified simple squamous epithelial cells that form the walls of blood vessels. The diameter of large arteries and veins can be made up of dozens of Endothelial cells, whereas the smallest capillary is formed by a single Endothelial cell folding onto itself to form the lumen of the vessel. These Central Nervous System microvascular Endothelial cells are extremely thin cells that are 39% less thick than muscle Endothelial cells, with a distance of less than a quarter of a micron separating the lumenal from the parenchymal surface. There are two main categories of transporters expressed by Central Nervous System Endothelial cells. The first is efflux transporters, which are polarized to the lumenal surface and transport a wide variety of lipophilic molecules that could otherwise diffuse across the cell membrane, toward the blood. Blood-brain barrier components diagram is shown in figure 1.

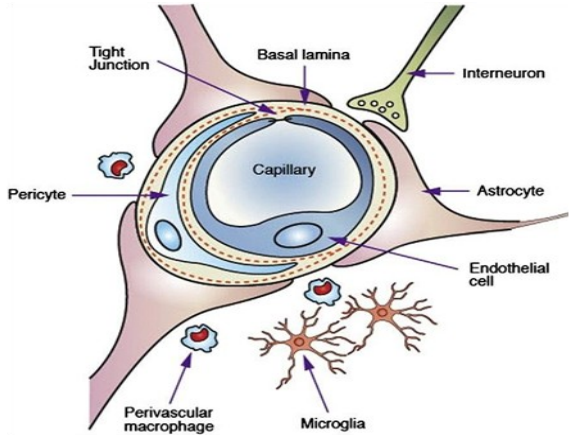

Figure :1 Blood-brain barrier components diagram

The strong interaction between cells tightens the gap between endothelial cells, and there is no pore structure on the surface of the cell membrane. Central Nervous System Endothelial cell. Other tissues have unique properties compared to Endothelial cell which permit them to strictly regulate the movement of molecules, cells and ions, between the brain and the blood. The Central Nervous System Endothelial cell is held in place by a solid junction (TJ), which places a significant limit on the flow of solvents. This strong paracellular and transcellular barrier forms a vascular cell, consisting of lumenal and abdominal components, such as that action between blood and brain are often tightly controlled

by normal cellular transport. Endothelial cells not only maintain Blood-Brain Barrier integrity but also act as a barrier to toxins and pathogens [21].

b: Astrocytes:

Astrocytes are a major glial cell type, which extend polarized cellular processes that ensheath either neuronal processes or blood vessels. Astrocytes play essential roles in various brain activities, in part by manipulating SLC (Solute carriers) functions. Despite the fact that most Solute carriers families have members expressed in astrocytes, the characterization of their functions remains at the initial stage and requires further investigation. Astrocytes are assisted to carry and shield the neurons through the regulation of the neurotransmitter and ion concentration in order to maintain a homeostatic balance in the central nervous systemmicrolevell, on the basis of the change in synaptic transmission, and regulation of the immune system and its interaction with endothelial cells, on the basis of their prediction endfeet on the basolateral side of the brain, the blood vessels [22]. Astrocytes form a bridge to neuronal signaling and the vasculature of the central nervous system. Astrocytes are mixed up in the maintenance of the integrity of the Blood-Brain Barrier mainly due to the release of active substances, in particular of the growth factor in this process. In addition, there is a complex relationship between astrocytes and blood vessels in the brain, which plays a key role in the maintenance of Blood-Brain Barrier function. Astrocytes have been identified as important mediators of Blood-Brain Barrier formation and function because of the ability of purified astrocytes to induce barrier properties in non-Central Nervous System blood vessels in transplantation studies.

c: Pericytes :

Pericytes are essential constituents of the brain capillary with different frequencies in different vascular beds. They are most abundant in the Central Nervous System, particularly in the retina. Pericytes are known to be involved in the vascular smooth muscle cells, major cellular components of the post capillary venule, and the blood vessels. It is closely related to endothelial cells, N-cadherin, gap junction, and tight junction, outside of the blood vessels, as well as the shares in the same basement membrane of endothelial cells. Pericytes also play essential roles in maintaining Blood-Brain Barrier integrity, aiding in angiogenesis, and microvascular stability. Pericytes may display phagocyting functions helping with the removal of toxic metabolites. Pericytes are involved in a number of important functions, while in a stroke, including the regulation of blood flow and Blood-Brain Barrier permeability, as well as the repair of the neurovascular unit [23].

d : Basement membrane :

The basement membrane contains Type IV collagen, laminin, and fibronectin. The extracellular matrix as a key component of the basement membrane, is composed of molecules, which are synthesized and secreted into the extracellular space. Fibronectin binds to the basement membrane into the surrounding tissue, and the extracellular matrix, and suggests a role in the maintenance of Blood-Brain Barrier functions. The basement membrane may be influenced by matrix metalloproteinases (MMPs). The degradation of the basement membrane components, in order to increase the permeability of the Blood-Brain Barrier, which results in swelling, bleeding, or even death may occur [24].

e: Neurons:

The nerve cells that remain near the blood vessels, and in order to make a connection with the endocyticend feet in the vicinity of the Blood-Brain Barrier. The nerve cells are rarely higher than in the 8 to 20 µm in the blood vessels of the brain, it is estimated that each neuron has capillary. In the vicinity of the Endothelial cell, which permits the neurons to respond to an alternating environment and, in particular, in relation to balance the ion. The nerve cells play an important role in the regulation of microvascular penetration, blood flow, interaction with the extrinsic source, and the liberation of substances to promote angiogenesis. The neurons help to increase the endothelial cells of the brain, culture, and assist in the synthesis of proteins in the synthesis and localization.

2.2. Physiological Properties of Blood-Brain Barrier:

The brain has an extensive network of blood vessels in the brain tissue which is consist of arterial and venous. However, most action takes place at the level of capillaries. The central nervous system is made up of neurons and glial cells in the vertebrates. However, neurons are not regenerative cells; therefore, it is important to maintain homeostasis to protect neurons. The Blood-Brain Barrier is a barrier to solute exchange between the brain and blood to store this micrmacroeco logical stance, which was discovered and named by biolbiologistslich and Goldman in the late 19th century. Blood-Brain Barrier is a series of physiological factors that may require to be activated (metabolic enzymes, transporters, Ts) or inhibited in Central Nervous System Endothelial cells. The Central Nervous System vasculature is the main gateway that controls access to blood-borne molecules in the brain, which is why it acts as a link between the brain and external influences. This immune barrier, which allows only the transport of selected cells from all parenchyma of the brain and endothelial cells (ECs), is understood as Blood-Brain Barrier [25]. The substrate formation of Blood-Brain Barrier is a neurovascular unit (NVU); a cellular association formed by a close association of the activity of Endothelial cells, astrocytes, pricandytes, and supported by other Central Nervous System cell types [26]. Endothelial cells in the Central Nervous System block cell transport by interlocking proteins forming hard pathways which are Tight Junction (TJs) , allowing the passage of metabolites and nutrients only by tightly controlled transport and restricting the entry of unwanted products by inhibited efflux carriers and transcytosis.

2.2.1: Regulation of the Blood-Brain Barrier formation and homeostasis

Blood-Brain Barrier is a potent compound that converts molecules between blood and brain in response to homeostatic correction in disease and health. Throughout life, the strength of the Blood-Brain Barrier is in keeping with the ever-changing changes in various body regions. The physical variability of Blood-Brain Barrier resilience under healthy conditions, **and therefore the** mechanisms that regulate how Blood-Brain Barrier structures tend **to revive** brain homeostasis **aren't** well understood. In this context, focuses on present knowledge of Blood-Brain Barrier's dynamic adaptation to respond to physical exchanges that include factors such as growth, pregnancy, sleep, aging, environmental pressures and dietary changes. Exploring these powerful Blood-Brain Barrier rules could open up new perspectives on understanding how systemic variables can change in dissimilar neuropathological regions and may reveal current therapeutic approaches. By embryonic stages, the fetus is exposed to a host of harmful substances that circulate

through the mother's bloodstream through the placenta, which forms a barrier between the blood and the placenta [27]. However, the Blood-Brain Barrier is earlier made up of embryonic levels and offers extra safety to the developing Central Nervous System. It is a critical phase of time when the body, including the mind, changes into adulthood. During puberty, there is an increase in follicle stimulating hormone and luteinizing hormone, which causes the production of sex steroids (testosterone and estradiol). Sex hormones trigger synaptogenesis and spinal repair and regulate brain growth, resulting in sexual cohesion in other brain regions during adolescence. Steroid hormones can cross the Blood-Brain Barrier one by one, due to their small size and lipid concentration. High radiology (magnetic resonance imaging) in humans has shown a progressive age increase in Blood-Brain Barrier stiffness. Similarly, Blood-Brain Barrier degeneration appears as the first biomarker of Alzheimer's disease.

2.2.2: Regulation of Barrier Properties during Angiogenesis

Angiogenesis contains cell proliferation, vessel proliferation, anastomosis formation, pruning and reconstruction, and the detection of endothelial quiescence Antigenic and differential function of endothelial progenitors determine the mechanisms of EPC-supported angiogenesis. In the brain, vascularization mainly occurs through angiogenesis and therefore the different cell communities involved in angiogenic events contribute to increased vessel growth, strengthening the cellular matrix, the establishment of the novel microvessels, and its maturity. barrier and access to adequate access selection and delivery function.

Angiogenesis continues to support growing tissues, but many blood vessels become quiescent during growth. Regeneration of quiescent vessels occurs only under certain conditions in adults, for example in the uterus and ovary, in the placenta during pregnancy, and in skeletal muscle to support muscle growth caused by exercise. Angiogenesis is also regenerated after injury to promote tissue repair by increasing vascular supply, but this response may be harmful, for example, to ocular pathologies such as proliferative diabetic retinopathy or a “wet” type of age-related macular degeneration, in which tissue ischemia leads in the formation of ectopic and leaky arteries. In addition, tumor angiogenesis can promote tumor growth, thereby contributing to the progression of cancer. In these diseases, neo-angiogenesis often leads to the formation of abnormal vessels with enlarged blood vessels. Although vascular stiffness is beneficial after severe tissue damage by the introduction of coagulation factors, antibodies, and cytokines, chronic exposure can cause pathological tissue edema. Angiopoietin has also been identified as a potent angiogenic factor during fetal vessel development. Ang-1 deficiency leads to embryonic nerve damage in the central nervous system (CNS) and many other parts of the body, due to improper interaction of the upper matrix of cells and supporting cells [28].

2.2.3: Regulation of the Blood-Brain Barrier by Pericytes

Pericyte cells are mural cells that come in the walls of the arteries under the vascular smooth muscle cellseries. Although these cells were discovered more than 100 years ago, pericytes rarely attracted attention because they were considered to be endothelial cells that support endothelial cells. Recent research has established that pericytes not only provide physical support to endothelial cells but also play critical roles in vessel function. In fact, pericytes form contacts that focus on endothelial cells at sites known as nail contacts. In these

contacts, pericytes are connected to endothelial cells through strong connections, gaps, and adhesions. Pericyte installation varies between different types of vessels. The ratio of pericyte-endothelial cells ranges from 1 : 100 in skeletal muscle to 1 : 1 in the retina. In general, vessels in the Central Nervous System show superior pericyte coverage, highlighting the importance of pericytes in the formation and maintenance of Central Nervous System vasculature

2.2.4: Regulation of the Blood-Brain Barrier by Astrocytes:

Astrocytes are also made by ACE-1 (angiotensin-converting enzyme-1), which changes angiotensin I to angiotensin II and activates angiotensin type 1 (At1) receptors that are shown by the Blood-Brain Barrier Endothelial cells. Angiotensin II strengthens the strengthening of vessels, and, in the Central Nervous System, activation of AT1 inhibits the entry of Blood-Brain Barrier and strengthens protein synthesis by their synthesis by promoting their uptake into lipid rafts. Perivascular cells, including astrocytes, secrete Ang1 (angiopoietins), and participate in the network process of Blood-Brain Barrier differentiation by promoting angiogenesis and reducing depressive-induced endothelial proliferation. This occurs with high regulation of junctional protein expression Unlike Ang-2, it is well known for being involved in the early stages of the mechanism of eliminating Blood-Brain Barrier damage in injuries and diseases.

Interestingly, when known Blood-Brain Barrier compromise factors such as vascular endothelial growth factor (VEGF) are linked to Ang1, barrier reliability is enhanced and security features are developed. Astrocytes also secrete angiogenic substances that promote blood vessel growth. During development, VEGF is essential for the survival of embryonic blood vessels, formation, and regeneration.

2.3: Crossing the Blood-Brain Barrier

Blood-Brain Barrier has a number of highly selective mechanisms for transferring nutrients to the brain. Structurally, the Blood-Brain Barrier (BBB) is that the most selective barrier that separates circulating blood from the fluid outside the brain cells within the Central Nervous System (CNS). The blood-brain barrier is made up of endothelial cells in the brain, which are connected by strong sides. The blood-brain barrier allows the passage of water, other gases, and lipid-soluble molecules by inconsistent circulation, as well as the selective transport of molecules such as glucose and amino acids essential for neural function. In addition, it inhibits the penetration of potential lipophilic neurotoxins in the form of an active P-glycoprotein. Active mobility conducts movement compared to the concentration gradient and requires ATP hydrolysis. The movement between cells is called cell proliferation. Paracellular transport is used to move material through the epithelium by the space between cells.

2.3.1: Passive permeability:

In general, a wide range of lipid-soluble molecules can diffuse passively through the Blood-Brain Barrier and enter the brain. There is a general correlation between the rate at which a solute enters the Central Nervous System and its lipid solubility. Molecular weight is another crucial factor in determining the free diffusion of small molecules across the Blood-Brain Barrier. For drugs to be freely filled with cerebral endothelium, an important requirement is the hydrophobicity of the molecule [29]. However, lipophilic molecules must have a molecular weight of less than 600 Da in order to penetrate into the membrane [30].

In addition, speculation about energy penetration involves the molecule's ability to combine with hydrogen ions. Thus, the replacement of hydrogen-binding groups by groups with no affinity of these ions increases the molecular lipophilicity. However, these substances can reduce the time it binds to plasma due to the rapid dissolution of highly lipophilic molecules and the slow melting of these substances into body fluids.

2.3.2: Carrier-mediated transport:

The Blood-Brain Barrier isolates the brain and limits the diffusion of many essential polar nutrients, including glucose and amino acids, which are essential for metabolism. Therefore, other routes for the essential nutrients to reach the brain are necessary. CMTs are encoded genes within the Solute Carrier (SLC) Transporter Gene Family. This includes more than 300 transporter genes encoding membrane-bound proteins that facilitate the transport of a wide array of substrates across biological membranes carriers are membrane-bound transport molecules that are much smaller than the endothelial cell, which is used to facilitate the transfer of nutrients such as hexose, nucleoside, purine base, amino acids to the brain. At least eight different systems of transport elements have been identified, each with a group of similar structures [31]. The mode of transport is the preferred substrate and the level of transport depends on the level of activity of the supervisor and may be influenced by competing and non-competitive inhibitors.

2.3.3: Active efflux transport:

The study of Blood-Brain Barrier detection methods can be very supporting for drug targeting (e.g., Paclitaxel) in the brain and achieving the expected Central Nervous System drug effect or reducing Blood-Brain Barrier drug infiltration to reduce Central Nervous System side effects. Within the Central Nervous System, multiple efflux pathways influence drug concentration in the brain. Several ATP-binding cassette (ABC) proteins are expressed on the luminal, blood-facing endothelial plasma membrane of the Blood-Brain Barrier. They are ATP-driven efflux pumps for xenobiotics and endogenous metabolites, which limit the permeability of multiple toxins, including therapeutic agent characteristics of the Central Nervous System are attributed to their high expression. Organic anion operators are also present in the Blood-Brain Barrier and prevent the binding of certain drugs and molecules to the brain. These systems are known as efflux transporters and include P-glycoprotein (P-gp) which is a glycosylated cell-derived component that is superior to the large ATP-binding cassette (ABC) carrier family. P-gp is also known as multidrug resistance protein (MRP) and is involved in the removal of drugs from the brain parenchyma, examples of which include chemotherapeutics, antibiotics, ion channel modulators, and immune suppressants. Other MRPs are expressed in brain microvessels, including BCRP and anti-cancer members of the organic anion transporter polypeptide (OATP) family, which regulate the efflux of anionic chemicals. All of these carriers are able to work in tandem, reducing the intake of many drugs in the brain and increasing their efflux from the brain [32].

2.3.4: Receptor-mediated transport:

The presence of peptide bonds limits the larger peptides and proteins from using the amino acid CMT systems to cross the Blood -Brain Barrier. However, specific neuro active peptides, regulatory proteins, hormones, and growth factors get the use of RMT systems to cross the Blood-Brain Barrier. These Large molecular weight solutes can enter the Central Nervous

System intact via endocytotic mechanisms in a process named transcytosis. Although most large blood-borne molecules are physically prevented from entering the brain by the presence of the Blood-Brain Barrier and TJs, specific and some non-specific transcytotic mechanisms exist to transport a variety of large molecules and complexes across the Blood-Brain Barrier Receptor-mediated transport is a process initiated by endocytosis of the ligand-receptor complex. Thereafter, it is involved in an endosomal chamber that can be transported to lysosomes or next to the cytoplasm for exocytosis. This type of transportation is power and temperature dependent. Receptors are able to transport large molecules such as proteins and small particles. To date, several receptors have been shown to live on Blood-Brain Barrier, including insulin, transferring, growth factors such as insulin (IGF), leptin, and low-density lipoprotein [33]. There are two types of vesicular transport systems; one is based on receptor-mediated transcytosis (RMT) and the other on adsorptive-mediated transcytosis (AMT). In RMT, macromolecular binds to ligands-specific receptors on the cell surface, which triggers an endocytotic event. Both receptors and their bound ligand cluster together, and a caveola are formed, which pinches off into a vesicle. Both ligands and receptors are internalized into the Endothelial cells and directed across the cytoplasm to be exocytosed at the opposite side of the cell.

2.3.5: Adsorption-mediated transport:

The surface of the plasma membrane of brain capillaries is poorly charged at body pH due to the presence of proteoglycans, mucopolysaccharides, and sulphate-and sialic acid containing glycoproteins and glycolipids. Adsorption occurs as a result of electrostatic interactions between a well-charged peptide amount and a poorly charged region in the plasma skin area. The type of transport is pure and undefined and occurs at a very low level under physical conditions. As a result of these structures, adsorption transport has been widely studied as a means of improving the delivery of peptides and proteins to the brain [34]. Molecules that enter the Blood-Brain Barrier through adsorption include various cationic proteins such as protamine, polylysine, glycatedalbin, histone and avidin [35].

REFERENCES:

[1] Ayodele A.T., Valizadeh A., Adabi M., Esnaashari S.S., Madani F., Khosravani M., Adabi M., (2017), Ultrasound nanobubbles and their applications as theranostic agents in cancer therapy: A review. *Biointerface. Res. Appl. Chem.*; 7, 2253–2262.

[2] Faisal N., Kumar K., (2017), Polymer and metal nanocomposites in biomedical applications. *Biointerface Res. Appl. Chem.*; 7, 2286–2294.

[3] Husain Q., (2017), Nanosupport bound lipases their stability and applications. *Biointerface Res. Appl. Chem.*; 7, 2194–2216.

[4] Kaur M., Singh G., Khanna K., Kaur N., (2015), Nanotechnology: A review. In Proceedings of the Second National Conference on Advances in Manufacturing Systems, S B S State Technical Campus, Ferozepur, India, 23–24 December.

[5] Abou el Ela A.E.S.F., El Khatib M.M., Salem-Bekhit M.M., (2017), Design, characterization and microbiological evaluation of microemulsion based gel of griseofulvin for topical delivery

system. *Biointerface Res. Appl. Chem*.; 7, 2277–2285.

[6] Fonseca-Santos B., Gremiao M.P.D., Chorilli M.,(2015), Nanotechnology-based drug delivery systems for the treatment of alzheimer's disease. *Int. J. Nanomed*.; 10, 4981–5003.

[7] Çetin M., Aytekin E., Yavuz B., Bozda'g-Pehlivan S., (2017), Nanoscience in targeted brain drug delivery. In Nanotechnology Methods for Neurological Diseases and Brain Tumors; Academic Press: Cambridge, MA, USA,; 117–147.

[8] Shatzmiller S., Lapidot I., Zats G., (2016), Blood-Brain Barrier crossing for therapeutic and diagnostic agents. *SM J. Neurol. Disord. Stroke*.; 2, 1012.

[9] Tucker I.G., (2011), Drug delivery to the brain via the blood-brain barrier: a review of the literature and some recent patent disclosures. *Ther Del*.; 2, 311–27.

[10] Gaillard P.J., Visser C.C., Appeldoorn C.C.M., (2012), Enhanced brain drug delivery: safely crossing the blood-brain barrier. *Drug Discov.Today Technol*.; 9, 155–60.

[11] Leonor P.D.M., Campia, I., Kopecka, J., Garzon R., Ghigo D., Rigant C., (2013),Nanoparticle-and liposome-carried drugs: new strategies for active targeting and drug delivery across blood-brain barrier. *Curr. Dru.gMetabol*. 2013; 14(6):625–40.

[12] Mandava N.K., Patel, M., Mitra, A,K., (2013), Advanced drug delivery to the brain. *Adv. Drug. Deliv*.; 405.

[13] Shah S.H., Shah M.J., Sharma J.R., (2009), Brain targeting: a novel drug delivery system. *J. Pharm. Res*.;2, 709–13.

[14] Kreuter J., (2013), Mechanism of polymeric nanoparticle-based drug transport across the blood-brain barrier (BBB). *J. Microencapsulation*.; 30, 49–54.

[15] Shah K., Abbruscato T., (2017), The blood-brain. In Conn's Translational Neuroscience: *Conn, P.M., Ed*.; 141–146.

[16] Obermeier B., Verma A., Ransohoff R.M.,(2016), The blood-brain barrier*: Elsevier*.; 133, 39–59.

[17] Khanna A.K., Farag E.,(2017), Blood-brain barrier. In Essentials of Neuroanesthesia: *Prabhakar, H., Ed.; Academic Press.;* 51–58.

[18] Grabrucke M. R., Chhabra R., Belletti D., Forni F., Vandelli, Barbara Ruozi M. A., (2013), Nanoparticles as Blood–Brain Barrier Permeable CNS Targeted Drug Delivery Systems: Top Med Chem. Springer- DOI: 10.1007/7355.

[19] Birgit O., Richard D., Richard R. M., (2013), Development, maintenance and disruption of the blood-brain barrier: Nature Medicine.; 19, 1584–1596.

[20] Paige D., Anthony D. H., Manasa., Shetty S.S., Raffic T., Srinivas M.,Rao B. S., (2021),Targeting receptor-ligand chemistry for drug delivery across blood-brain barrier in brain diseases: *Life Science.;*274,1.

[21] Abbott N.J., (2013), Blood-brain barrier structure and function and the challenges for CNS drug delivery: *J*

Inherit Metab Dis.; 36,437-49.

[22] Arellano R., Parpura J.J., Zorec V., Verkhratsky R. A., (2016), Astrocytes in physiological aging and Alzheimer's disease: *Neuroscience*.; 323, 170–182.

[23] Liu S., Agalliu D., Yu C., Fisher M., (2012), The role of pericytes in blood -brain barrier function and stroke: *Curr Pharm Des*.;18,3653-62.

[24] Thomsen M.S., Routhe L.J., Moos T., (2017), The vascular basement membrane in the healthy and pathological brain: *J Cereb Blood Flow Metab*.;37,3300-17.

[25] Langen, U.H. et al., (2019), Development and cell biology of the blood-brain barrier: *Annu. Rev. Cell Dev. Biol*.; 35, 591–613

[26] Segarra, M. et al., (2019), Neurovascular interactions in the nervous system: *Annu. Rev. Cell Dev. Biol*.; 35, 615–635.

[27] Goasdoue, K. et al., (2017), Review: The blood-brain barrier; protecting the developing fetal brain: *Placenta* .; 54, 111–116 .

[28] Lee H, S., Han J., Bai H. J., and Kim K. W., (2009), Review: Brain angiogenesis in developmental and pathological processes: regulation, molecular and cellular communication at the neurovascular interface: *The FEBS Journal*.; 276, 4622-4635.

[29] Koziara J.M., Lockman P.R., Allen D.D., Mumper R.J., (2006) The bloodbrain barrier and brain drug delivery: *J Nanosci Nanotechnol* .; 6, 2712-35.

[30] Dove A.,(2008), Breaching the barrier: *Nat Biotechnol*.; 26, 1213-5.

[31] Tsuji A., Tamai I.,(1999), Carrier-mediated or specialized transport of drugs across the blood-brain barrier: *Adv Drug Deliv Rev* .; 36, 277-90

[32] Zlokovic B.V.,(2008), The blood-brain barrier in health and chronic neurodegenerative disorders: *Neuron*.; 57, 178-201.

[33] Scherrmann J.M., (2002), Drug delivery to brain via the blood-brain barrier: *Vascul Pharmacol* .; 38,349-54

[34] Lalatsa A., Andreas G., Schatzlein., Ijeoma F., Uchegbu.,(2014) Strategies To Deliver Peptide Drugs to the Brain: Molecular Pharmaceutics.; 11,1081-93.

[35] Chen Y., Dalwadi G., Benson H., (2004), Drug Delivery Across the Blood-Brain Barrier: Current Drug Delivery.; 1, 361-76.

* * * * *