Bioinspired Nanocarriers: The Future of Targeted Cancer Treatment – An Overview

PREMA RATHINAM[1], SELVA BHARATHI SARAVANAN[2], SENTHILKUMAR CHELLADURAI[3], PREM KUMAR PANNEER PANDIYAN[4], SARAVANAN GOVINDARAJ[5], BALAJI PANDIYAN[6], KIRUTHIGA NATARAJAN[7], NANDHINI SUBRAMANIAN[8], MAMATHA VENKATASAMY[9]

[1, 2, 3, 8, 9]Department of Pharmaceutics, Sri Shanmugha College of Pharmacy, Salem, Tamilnadu.

[4]Department of Pharmaceutics, Tagore College of Pharmacy, Rathinamangalam, Chennai, Tamilnadu.

[5]Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai, Tamilnadu.

[6]Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai, Tamilnadu.

[7]Department of Pharmaceutical Chemistry, KMCH College of Pharmacy, Kalapatti road, Coimbatore, Tamilnadu.

Abstract*— Cancer is the second-leading cause of death in the world, and the survey conducted by the World Health Organization (WHO) says that cancer is the first and second-leading cause of death in 183 countries. The initial diagnosis of cancer can significantly improve patient survival. Conventional cancer therapies like surgery, radiotherapy, and chemotherapy have so many hurdles, including a lack of specificity and the formation of drug resistance. Nanoparticles (NPs) can be the solution to all the problems. NPs can be designed for targeted drug delivery and improve the solubility, stability, and half-life of anti-cancer drugs. Biomimetic nanoparticles (NPs) can mimic the action of the biological material, which improves biocompatibility and reduces the immune attack. These include cell membrane-coated nanoparticles (NPs) and natural protein-based nanoparticles (NPs). For example, RBC membrane-coated NPs can escape detection by the immune system, stay in the blood stream for a longer duration, and deliver the anti-cancer drug to the tumor site. Similarly, WBC membrane-coated NPs can naturally interact with the immune system for drug delivery and help with treatment by activating the immune system to fight against cancer. Even more, cancer cell membrane-coated NPs and albumin-based NPs have unique advantages for targeted drug delivery and the treatment of cancer. Further research on the biomimetic NPs shows their one more unique ability to cross the blood-brain barrier (BBB) and is essential for targeted drug delivery for brain diseases.

***Index Terms*- Biomimetic nanoparticles (NPs), Biocompatibility, Chemotherapy, Radiotherapy.**

I. INTRODUCTION

Cancer is the second-leading cause of death around the world after CVS diseases. In men, the most common cancers are prostate, lung, colorectal, and bladder. In women, the most common are breast, lung, colorectal, uterine, and thyroid. The researchers found that different stages of cancer involve several gene mutations. An earlier diagnosis of cancer can increase the life span of patients [1]. Most definitions of cancer broadly conform to the current NCI definition: "Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body" [2]. Researchers have identified more than 100 different types of cancer [3]. According to the Global Cancer Observatory, around 19.3 million cancer cases were reported worldwide in 2020. India has the third-highest number of reported cancer cases. In 2022, India had an estimated 1.4 million new cancer cases. In India, 1 in 10 people has the possibility of developing cancer. Lung cancer is the most common in men, and breast cancer is the most common in women. The Global Cancer Observatory predicts that India will reach 2 million in the year 2040 [4]. Patients with cancer can be treated with different clinical methods, like radiotherapy, chemotherapy, and surgery. Based on the tumor location, size, and medical history of the patient, decides the mode of treatment [5]. The creation of a new revolution in neoplastic cancer or targeting drugs depends on the pathways and characteristics of different tumor

entities. We can see cancer treatment modalities by dividing them into conventional (traditional) and advanced, novel, or modern categories. In this era worldwide, over half of all ongoing medical treatment trials are focusing on cancer treatments [6]. The traditional cancer treatment is surgical removal of the tumor followed by chemotherapy and localized radiotherapy. Of these modalities, surgery is most effective at an early stage of disease progression. Radiation therapy can damage healthy cells, organs, and tissues. Although chemotherapy has reduced morbidity and mortality, virtually all chemotherapeutic agents damage healthy cells, especially rapidly dividing and growing cells [7]. If the tumor cannot be removed surgically and starts to spread to other organs, then chemotherapy is the only option to control the spreading and reduce the size of the tumor [8]. Chemotherapy is a kind of oncology treatment that involves injecting one or more cytotoxic drugs into the bloodstream to kill the uncontrolled proliferating cancerous cells, especially when used as an adjuvant for surgery. Most of the chemotherapy drugs attack the actively reproducing cell, and some of them attack the particular phase of cell reproduction [3]. In the advanced stages of cancer, chemotherapy is used as induction therapy with the aim of reducing the tumor volume as much as possible and achieving clinical effects ranging from symptom relief to cure, depending on the tumor type. In adjuvant therapy, chemotherapy is added after controlling the primary tumor with, e.g., surgery or radiotherapy, with the aim of eradicating any tumor cells that might have escaped from the primary tumor and could regrow to form metastases in the future [9]. There are various excellent and potent chemotherapy drugs available, but the efficiency of those drugs is limited by their inability to reach the cancerous site [10]. Most of the chemotherapy agents are rapidly diffused in our whole body; only a small amount of the agents reaches the cancerous site, which causes lower efficiency. Because of these reasons, a higher dose is required to get the expected therapeutic effect, but due to the higher dose, the toxicity of the drugs might increase [11]. The primary drawback of chemotherapy is that the cytotoxic drug cannot differentiate between cancer cells and normal cells; it randomly damages both cancer and normal cells, and due to that, the patient gets more adverse effects [12]. For example, Paclitaxel is one of the most potent anti-cancer agents but causes serious hypersensitivity reactions, nephrotoxicity, and neurotoxicity [3]. One of the second major obstacles in the treatment of cancer is the development of resistance. The currently available chemotherapy agents are forming resistance during the course of treatment, which makes the treatment more and more complicated [13]. Cancer cells develop resistance to chemotherapy drugs due to changes in their genes and epigenetics, and interactions with their environment. These factors make it challenging to create more effective treatments [14]. P-glycoprotein (P-gp) is the active transporter mostly overexpressed in cancer cells, which plays a key role in the formation of multidrug resistance (MDR). It pumps out the anti-cancer drug from the cancer site, reducing the intracellular accumulation and decreasing the efficacy of chemotherapy. Not only that, but it also protects the cancer cells from apoptosis [15, 16]. The limitation of the current chemotherapy forces researchers to find any solution, leading to continuous research in nanotechnology. Researchers believe that nanoparticles can address and rectify these kinds of limitations.

II. NANOTECHNOLOGY ON CANCER TREATMENT

The primary drawbacks of chemotherapy are its lack of specificity, which makes it more toxic to healthy cells and tissues, and the development of resistance to the drug. Utilizing nanoparticles can solve both major issues [17]. The nanoparticles are very promising tools for cancer treatment due to their special capacity and properties. They help in several ways against the cancer disease, and few are listed below:

Targeted drug delivery: The NPs can be designed to target cancer cells, which will help us avoid the unwanted damage to healthy cells and tissues and minimize the toxicity produced by the drug. Due to the nanosize range, the NPs target the tumor site by taking advantage of enhanced permeability retention (EPR), which is usually called passive targeting. Additionally, the NPs target the cancer cells through an active targeting mechanism that utilizes the ligand (or) receptor that is present or over expressed in the cancer cells [18, 19, 20].

Improving the drug delivery: NPs can improve the delivery of anti-cancer drugs by improving their solubility, stability, and half-life. Most of the anti-cancer drugs are hydrophobic in nature; their hydrophobic nature poses safety risks during intravenous (IV) administration. Loading the anti-cancer drug into the NPs improves the solubility of the drug. These allow controlled and targeted drug releases at the tumor site [21, 22].

Overcoming the resistance: One of the major challenges in cancer treatment is multi-drug resistance. NPs overcome the resistance using the efflux transporter and delivering the drug into the cancer site [23]. The major reason behind the formation of resistance is the arising of P-glycoprotein, but recent studies explain that the NPs reach the cancer site without activating the P-glycoprotein, which increases the intracellular accumulation of drugs in the cancer site [24].

Diagnosis and imaging: Traditional cancer diagnosis has been aided by the application of nanoparticles (NPs), which have made the process easier and faster. NPs can be designed for carrying imaging agents, which helps in monitoring cancer, and the early detections are very crucial for the treatment [25].

III. LIMITATIONS OF NANOPARTICLES IN CANCER TREATMENT

NPs hold great potential against cancer diseases; they overcome many limitations produced by traditional chemotherapy, like drug resistance, target delivery, reducing toxicity, enhancing solubility, etc., but the number of NPs-based drug approvals for clinical use remains low [21]. The NPs fulfil several requirements until the many functional responses of our body determine the therapeutic efficacy of the nanodrug. The major problem causing this is that the NPs can trigger the immune response. If the immune system is triggered, then the defence system clears the NPs too quickly, which reduces the drug's reach at the tumor site. Some of the research studies explain that the immune system recognizes the NPs and tries to remove them from our body. Due to this, the circulation of NPs in the blood is reduced, which means the NPs do not reach the site of the tumor, particularly in areas with low blood supply [22]. To avoid unwanted immune clearance, the researchers developed many strategies, and one of the most common is to extend the blood circulation and restrict the immune response. The NPs surface is coated with polyethylene glycol (PEG) [27]. Initially, the PEG-coated NPs showed a very good result and gave us new hope in the battle against cancer, but the continuous research on the PEG-coated NPs made us disappointed. Yes, the repeated administration of PEG-coated NPs caused the production of specific antibodies (IgM) against PEG, which made the liver clear the NPs from the body too fast [28]. There is still need to create a new way to produce the NPs which will solve this kind to issue. For this reasons, most recently, the biomimetic nanoparticles was introduced.

IV. INTRODUCTION TO BIOMIMETIC NPs

The term biomimetic originate from the Greek word “bios” means life and “mimetic” means copy or mimicry [29]. Biomaterials capable of mimicking the biological features and functions of native cells integrate or fabricate the surface of biomimetics nanoparticles, an emerging class of nanoparticles. Biomimetic nanoparticles possess greatly improved biocompatibility, high target specificity, a long retention time and minimal undesired immune responses [30]. Biomimetic NPs are a successful approach to handling cancer because of their ability to enhance the efficacy of therapeutics and escape immune system identification. By mimicking the structure of the biological material, the NPs are able to deliver the drug at the site of the tumor. There are various types of biomaterials used to coat the NPs, including cell membranes like RBC’s, WBC’s, platelets, and even cancer cells. There are also so many options available, like monoclonal antibodies, natural proteins, viral capsids, and synthetic biomaterials [31]. Biomimetic NPs take advantage of both cell membranes and synthetic NPs and are distinguished by three main features: prolonged circulation in the bloodstream, specific binding, and reduced toxicity [32]. Further, the biomimetic NPs can avoid immune identification, and the overall review focuses on the advancement of biomimetic NPs and their ability to use biomimetic nanoparticles as a novel platform for targeted cancer therapy and to highlight their unique characteristics. The biomimetic NP’ are majorly classified into two types:

- Cell membrane coated Nanoparticles.
- Natural protein based Biomimetic Nanoparticles.

V. CELL MEMBRANE COATED NANOPARTICLE

Cell membrane-coated NPs have emerged as a promising way for cancer treatment due to their special ability to mimic the nature of cell function; thereby, they enhance biocompatibility, targeting specificity, and therapeutic efficacy. These kinds of NPs are nothing hard; just the NPs are entirely wrapped with the cell membranes, which can avoid immune recognition and allow them to accumulate more efficiently in the tumor site. The cell membrane coated NPs were first introduced to increase the duration of NPs circulation in the blood stream by RBC's membrane, which shows the "stealth" properties of the synthetic NPs from the immune system. [33]. Cell membrane-coated NPs are innovated to tackle the limitations, particularly for better drug delivery. They are very potent because they are highly biocompatible, can stay in the body for a longer period of time, have lower toxicity, can target a specific area, escape from the immune system, and are stable. These characteristics make them a promising choice for targeted therapy for cancer [34]. Here, we discuss the recent advancements in this field, focusing on different types of cell membranes used for coating NPs and their applications in cancer treatment.

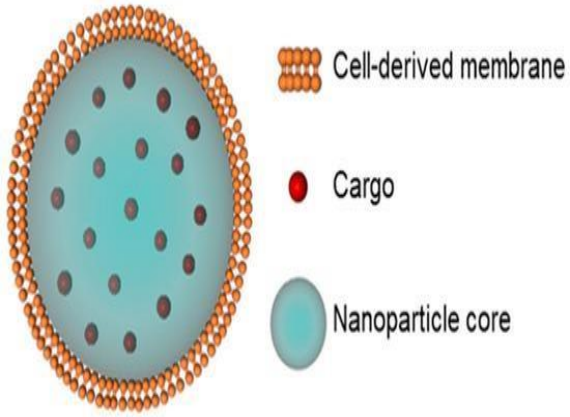

Figure 1.1: Representing the Cell Membrane Coated NPs [46].

Red Blood Cell Membrane Coated NPs: These RBC's cell membrane-coated NPs are the first innovative type of CMC NPs. Our immune system recognizes the oxygen that the RBC's cells naturally carry and can easily avoid unwanted immune clearance [35]. These happen due to the presence of a protein called CD47 in the cell membrane. One of the most important jobs of CD47 is to send a "do not eat me" signal to the macrophages, which are immune cells. These signals are transmitted through a receptor called SIRPα on the surface of macrophages. The studies explain that the immature RBS's have CD47 on their membrane. CD47 binds to the SIRPα on macrophages, which prevents the eating of RBC's from macrophages [36]. In 2011, a study was conducted between the two types of NPs, one coated with PEG and the other on the RBC's membrane. The result showed that the RBC's coated NPs circulate for a longer duration in the blood stream (40 hrs) compared to the PEG-coated NPs, which circulate for 16 hrs in the blood stream. The study showed that the RBC-coated mice were better able to avoid immune reorganization and fast clearance from the body. Since the use of RBC's coating has very good targeted drug delivery [37], these kinds of nanoparticles (NPs) can enhance the tumor-targeting ligands to increase the specificity for cancer cells and show better drug delivery. Conjugating the RBC membrane-coated NPs with other types of cell membranes can increase the targeting capacity and therapeutic efficacy [38]. RBC membrane-coated NPs can be loaded with many types of therapeutic agents, like chemotherapeutic drugs, photothermal agents, and immunostimulants, to achieve synergistic effects in cancer therapy. Combination therapies like chemo-photothermal therapy provide controlled release and enhance the accumulation of drugs at the tumor site [39]. Collaborating the imaging agents with the RBC membrane-coated NPs gives better imaging and diagnosis of tumors and is also useful for monitoring treatment efficacy. Additionally, some of these kinds of NPs are designed to modulate the immune system, enhancing its natural ability to fight against cancer through photodynamic immunotherapy [40]. Researchers have developed the idea that the RBC membrane-coated nanoparticles are used to relieve tumor hypoxia, which is a common problem in solid tumors due to low blood flow and irregular blood vessel growth. In this study, they employee perfluorocarbon to dissolve the oxygen, which is an organic molecule, and it is safe to use. The perfluorocarbon was encapsulated inside PLGA NPs,

then coated with RBC membranes. When these NPs were injected into the mice's bodies with breast tumors, they successfully relieved hypoxia in the tumors within 8 hours. This was confirmed by tumor histology. The mice were treated with radiotherapy 24 hours after the injection. The results showed that the pre-treated mice with the NPs had better results, as the NPs improved the power of the radiotherapy and suppressed tumor development more effectively than radiotherapy alone [31]. This illustration demonstrates how combining radiation and membrane coating-based treatments might improve the therapeutic efficacy even further.

White Blood Cell Membrane Coated NPs: Leukocytes, or white blood cells, are some of the other most crucial components of blood cells. Tumor growth is aided by a variety of inflammatory cell populations, such as mast cells, eosinophils, neutrophils, dendritic cells, macrophages, and eosinophils [41]. White blood cell-derived NPs (WBC-NPs) are a special type of carrier that is used for drug delivery because of their natural ability to interact easily with the human biological system, allowing them to more effectively target a specific site and avoid the unwanted toxic effect. These NPs prolong circulation in the blood and enhance tumor targeting capacity because they can mimic the properties of the WBCs [42]. Additionally, WBC-NPs can influence the bodies deafens system in two ways: they can act as nanocarriers and also stimulate the immune system to fight against cancer, and they escape from immune detection, reducing the elimination by the immune system and thus enhancing the efficacy of the encapsulated drug [43]. Moreover, the WBC-NPs multitalented and they can use for combination therapies, such as photothermal therapy and chemotherapy, to improve therapeutic outcomes. These NPs can be loaded with different therapeutic agents, making them more potent in the targeting the cancer tumor [44]. By using natural cell membranes to coat the NPs, their compatibility with the body is getting increased, and toxicity gets reduced, making them as a safer for in vivo uses.

Overall, the characteristic of the WBC-NPs make them as a potent tool in the battle field of cancer treatment [45].

Cancer Cell Membrane Coated NPs: The cancer cell membrane has unique properties for coating the NPs used in cancer treatment because they are very much convenient to culture in large amount for the membrane collection and they can self-target cancer cells. These special properties allow the cancer cell membrane-coated NPs to specifically target the cancer tumor and enhance their binding and uptake. CCNPs have a longer circulation time in the blood stream due to their ability to avoid immune identification, making them more potential for drug delivery, phototherapy, tumor imaging, and immune modulation. And also, the nanocarrier can be designed with different therapeutic agents, making the CCNPs more significant in cancer treatment [46]. For example, the NPs made by PLGA are loaded with the potent anti-cancer drug used for many cancers, like breast and ovarian cancer, doxorubicin (DOX). The PLGA NPs with DOX are then coated with liver cancer cells and injected into mice with HepG2 tumors. The results show that the CCNPs show less toxicity compared with free-injected DOX. This reduced toxicity happens due to the enhanced accumulation of DOX in the tumor area, which reduces the accumulation at the off-targeting site and prevents premature drug release [47]. In the other study, the researchers loaded the one more potent anti-cancer drug palitaxel (PTX) in the NPs made by certain polymers and coated them with membranes from 4T1 mouse breast cancer cells. This cancer cell coated PTX-loaded NPs were injected into mice with highly metastatic 4T1 tumors. These special-type NPs target and slow the growth of the primary tumor and spread in the metastatic nodules of mice. They were 6.5 times more potent at reducing tumor spreading compared to uncoated NPs [48]. The example of a study involving cancer cell membrane-coated NPs shows very good results, proving them to be a potent candidate for cancer treatment.

VI. NATURAL PROTEIN BASED BIOMIMETIC NANOPARTICLES

Proteins are an essential component of the human body and are mostly involved in most cellular processes. They play an essential role in both the biological and manufacturing processes; they can work as a fundamental material for preparing the NPs. The protein NPs are very small, and they enter the cell through a process called endocytosis. They offer

several advantages, like biodegradability, stability, surface modification, precise size control, and lower toxicity issues such as immunogenicity. Moreover, protein NPs can increase stability, activity, and half-life by protecting them from renal elimination and enzymatic degradation [49]. There are different types of proteins that have been used in NPs, like albumin, ferritin, and lipoproteins. It is an effective tool for targeted drug delivery, and the study revealed that natural proteins have a greater potential for targeting specificity, sustained drug effects, drug stability, and synergistic effects [50].

Albumin Based NPs: Serum albumin is a natural protein for the fabrication of NPs, and it is the most abundant protein in the blood. Albumin NPs have high favorability for drug delivery in cancer treatment, and they show good biocompatibility, biodegradability, and non-immunogenicity [51]. Fabricating the NP surface with albumin can protect them from being recognized and cleared by the mononuclear phagocytic system (MPS), which is responsible for their transport to tumors [52]. Multifunctional albumin-based nanoplatforms have been created for combining imaging and therapeutic agents, which improve cancer diagnosis and treatment. While techniques like pH-responsive and photodynamic-triggered release can be used for better drug release, which lowers the toxicity, The performance of the drug can be improved overall by using human serum albumin fragment nanoparticles (NPs) [53]. Which have drug loading capacity and produce the controlled drug release. Emulsion-solvent evaporation is one of the methods for producing the HSA-NPs since it shows excellent drug loading efficiency and efficient in vitro release [54]. Most of the anti-cancer drugs have low water solubility and are mostly hydrophobic in nature. However, injecting hydrophobic drugs via IV causes major safety issues, like embolizing blood capillaries. Albumin NPs can help solve these problems by increasing the solubility of the drugs. And additionally, both hydrophilic and hydrophobic drugs can be loaded into the albumin NPs [55]. The Albumin NP's target the cancer cells by both the mechanism of active and passive. Passive targeting is achieved by the enhanced permeability retention (EPR) effect, and active targeting is possible through the Albumin Binding Protein (ABP) receptor, which is present in cancer cells [56]. Recent studies show that cancer tumors are overexpressed with ABP, such as secreted proteins rich in cysteine (SPARC) and glycoprotein-60 (gp-60) [57]. In order to achieve the biomimetic transport mediated through the SPARC and glycoprotein-60, such as secreted proteins rich in cysteine (SPARC) and glycoprotein-60 (gp-60), a low-molecular weight protamine known as a cell-penetrating peptide was used to create the surface of the BSA nanoparticles. LBSA nanoparticles, which were co-encapsulated with PTX and ferentinide, were created by coating low-molecular weight protamine-coated BSA nanoparticles [58]. For example, Abraxane, a solvent-free nanoversion of Taxol, was created by NAB technology, and it was the first albumin-based NP marketed by American Bioscience in 2005 for breast cancer treatment in the US. It is an FDA-licensed drug that is also used for pancreatic and non-small-cell lung cancer. Abraxane quickly dissolves in the blood stream after administration, forming soluble albumin-bound PTX complexes. These complexes reach the tumor site due to the EPR effect and ABP receptors like gp60 and SPARC [59].

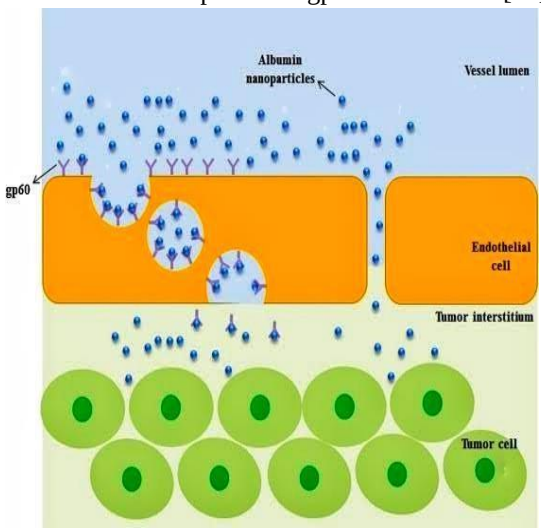

Figure 1.2: Uptake of the albumin nanoparticles by EPR effect and also by the glycoprotein gp60 [59].

VII. CROSSING OF BLOOD BRAIN BARRIER (BBB)

Brain tumors are the main cause of disability worldwide, and very few medications have been developed to treat brain tumors. Different reasons are behind restricting their therapeutic efficacy, and the most important hurdle is the blood-brain barrier (BBB) because the drugs are unable to pass the BBB [59]. The

BBB is the protective layer made up of endothelial cells, pericytes, and astrocytes, which control the substance's transport to the brain. The direct penetration of BBB is possible for small and fat-soluble molecules with a molecular weight of less than 450. Nutrients like glucose, amino acids, and iron pass through the BBB through specific transporters or receptors. The BBB protects the brain from harmful substances and allows only the required substances [60].

By Natural Protein Based NPs: Albumin is an essential nutrient, but it is usually does not entre the brain but it is heavily taken by the growing tumors for their rapid growth and energy. The ABP like SPRAC and gp-60 are responsible for the absorbing the albumin for the tumor and this ABP are overexpressed in the tumor site which help for their massive growth, making possible targeting the tumor. So through the concept the employing albumin nanoparticles used for treatment of brain cancer and based on this concept various study was conducted. The results of these study show a promising strong intracellular delivery, intratumoral infiltration, and BBB penetration [58].

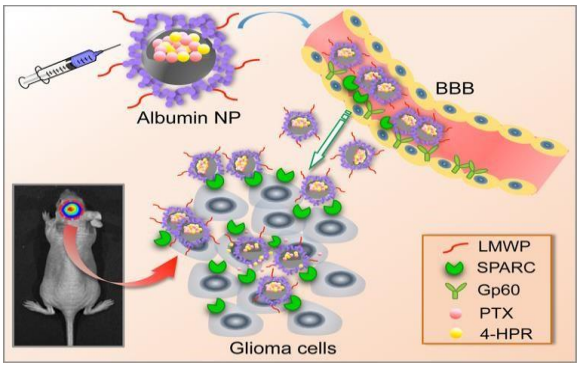

Figure 1.3: By targeting ABPs such gp60 and SPARC, the BBB piercing NPs are able to enter brain tumor cells [58].

By Cell Membrane Coated NPs: Gram-negative Escherichia coli K1 (EC-K1) can penetrate the BBB and cause neuronal meningitis in the brain. A protein called OmpA, which is present in the surface of EC-K1, which helps this process. It contains 325 amino acid proteins with 8 transmembrane domains and 4 extracellular loops. OmpA interacts with a protein called gp96, also known as GRP94, which is present on the surface of BBB endothelial cells. The surface of OmpA binds to the gp60 on the BBB, allowing the EC-K1 to cross the BBB. Based on the concept, the outer membrane of EC-K1 has the potential to be used for brain diseases. With the inspiration of cell membrane-coated NPs, the EC-K1 membranecoated NPs can penetrate the BBB and deliver the drug to the brain. However, the use of the EC-K1 outer membrane for brain-targeted drug delivery has not received so much attention [60].

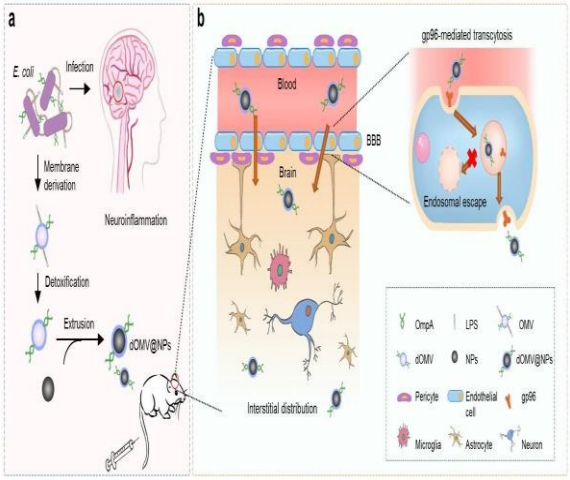

Figure1. 4: Mechanism of BBB Penetration by EC-K1 Membrane Coated NPs [60].

CONCLUSION

The biomimetic NPs have shown greater promise in cancer treatment. These vectors produce significant improvements in drug targeting cancer cells, stay in the blood longer duration, and avoid the attack produced by the immune system. Their unique potential in brain tumor therapy is immense and opens up a new way for more effective and targeted treatments. The ability of these NPs to mimic the activity of natural biological systems, in contrast to conventional therapies, facilitates targeted drug delivery and decreases side effects, leading to better overall therapeutic efficacy. WBC membrane-coated NPs are examples of compounds that stimulate the immune system to fight cancer cells, while RBC cell-membrane NPs can evade immune systems' detection. The solubility of natural protein-based NPs, such as those produced from albumin, is enhanced, and biomimetic NPs' ability to impact cancer treatment is being promoted through dual targeting mechanisms. Further studies are needed to tackle problems like

improving targeted effectiveness, reducing immune clearance, and prevent the formation of drug resistance. Biomimetic NPs could revolutionize cancer treatment by providing patients with safer and more effective options through ongoing research...

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