

Advancements in Nano Drug Delivery for Targeted Treatment of Brain Tumors: Breaking Barriers for Enhanced Therapeutic Outcomes

Deepak Kumar Sahu¹ and Harish Jaiswal²

Abstract

Brain tumors provide a health obstacle characterized by an intricate past closely linked to medical progress. The need to tackle this matter stems from the significant influence of brain tumors on cognitive performance and general welfare. The current treatment options face difficulties, mainly because of the complex blood-brain barrier and the need for accurate medication administration at the tumor location. This research promotes the use of Nano Drug Delivery for Targeted Treatment of Brain Tumors (NDD-T2BT), acknowledging the crucial importance of nanotechnology in addressing these difficulties. NDD-T2BT utilizes sophisticated nanocarriers to augment medication concentration, specifically at the tumor site, provoke immunological responses, and promote the permeability of the blood-brain barrier. The proposed method, characterized by the mean values of necessary measurements (62.87% drug concentration, 1888.78 cells/ μ L immune response activation, 0.0910 cm/s barrier permeability, and 91.23% tumor cell viability reduction), effectively overcomes the shortcomings of current therapies. The results highlight the potential of NDD-T2BT to transform the treatment of brain tumors by providing a complete and precise strategy that shows promise for improved therapeutic outcomes.

Keywords: Brain Tumors, Nano Drug Delivery, Blood-Brain Barrier, Targeted Treatment.

Introduction to Brain Tumors and Nano Drug Delivery

Brain tumors, an intricate and demanding group of cancerous growths, have consistently posed a significant medical challenge throughout history [1]. Historical archives include accounts of symptoms matching those of brain tumors dating back to ancient times. However, the comprehension of these disorders and the development of appropriate therapies have seen advancements over the years [2]. The 19th century was a significant era in the development of neurosurgery since it saw the emergence of early efforts to remove tumors. In the 20th century, progress in diagnostic imaging, including the emergence of Computed Tomography (CT) [3] and Magnetic Resonance Imaging (MRI) [4], allowed for the accurate detection and characterization of brain tumors.

There has been an increase in the occurrence of brain tumors throughout time, which has had a significant effect on the overall well-being of the population. Recent figures indicate that there are over 700,000 new instances of brain and central nervous system tumors identified worldwide every year, leading to rates of illness and death. The need for creative and focused treatment approaches is of utmost importance, considering the complex

¹ Assistant Professor, Department of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh, India. ku.deepakkumarsahu@kalingauniversity.ac.in, Orcid: <https://orcid.org/0009-0007-2995-1175>

² Assistant Professor, Department of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh, India. ku.harishjaiswal@kalingauniversity.ac.in, Orcid: <https://orcid.org/0009-0000-8183-4944>

characteristics of the brain and the obstacles presented by the blood-brain barrier (BBB) in the transportation of drugs.

Nano Drug Delivery is a promising and innovative field in the fight against brain cancers [5]. Nano-drug delivery systems, including polymers, lipids, metals, and other substances, provide distinct benefits in overcoming the constraints of traditional drug delivery techniques [6]. The significance of nanotechnology in brain tumor therapy rests in its capacity to augment medication delivery efficiency, boost therapeutic results, and alleviate systemic toxicity. These devices use Enhanced Permeability and Retention (EPR) effects to deliver passive targeted medication to the tumor location.

The current approaches encounter significant obstacles. The Blood-Brain Barrier (BBB), composed of endothelial cells in cerebral microvessels, impedes transporting therapeutic agents to the brain [7]. Although there have been improvements in medication delivery, it is still crucial to develop effective methods to increase the capacity of nanocarriers to pass across the BBB. The systemic pathway, aided by nanocarrier modification, is widely recognized as the most prevalent and extensively investigated method. Ongoing research investigates Receptor-Mediated Transcytosis (RMT) and Adsorption-Mediated Transcytosis (AMT) [8].

The technological and numerical factors underscore the need for progress in brain tumor therapy. The fatality rate for malignant brain tumors remained high, with a five-year survival rate varying from 20% to 30%, emphasizing the urgent need for more efficient treatments. Moreover, the difficulties posed by drug resistance in chemotherapeutic treatments and the intrinsic intricacies of the tumor microenvironment necessitate the development of novel therapies. The use of nano drug delivery systems has the potential to improve the effectiveness of brain tumor therapy by increasing the therapeutic index, minimizing systemic toxicity, and overcoming drug resistance. As the research explores the intricacies of nano-drug delivery for brain tumors, it is crucial to understand the complex relationship between scientific advancements, clinical obstacles, and the pressing need for successful treatment approaches.

The main contributions are

- **Improved Targeting Accuracy:** The suggested approach employs nanotechnology to target brain tumor cells precisely, reducing harm to healthy organs.
- **Immune Modulation:** Stimulating dendritic cells and controlling macrophage polarization improves the body's ability to fight against tumors.
- **Innovative nanocarrier techniques** enable effective medication delivery across the blood-brain barrier, overcoming this challenge.
- **Synergistic Impact:** This approach combines the direct elimination of tumor cells with the induction of immunogenic cell death, resulting in enhanced therapy effects.

The following sections are listed in the given manner: Section 2 examines the current state of research in the literature review. Section 3 introduces the concept of Nano Drug Delivery for Targeted Treatment of Brain Tumors (NDD-T2BT). Section 4 provides a detailed examination of the simulation study and the results of implementing the recommended strategy. Section 5 summarizes the findings and provides an overview of the potential following directions for the study.

Literature Summary

This section examines prior research, investigating the present understanding and progress in treating brain tumors using different drug administration techniques, specifically emphasizing nanotechnology. This text summarizes the difficulties and knowledge obtained from the literature, establishing the basis for the following conversation.

The literature assessment conducted by Hersh et al. focuses on the progress made in nanoparticle technology for delivering drugs in neuro-oncology [9]. The Nanoparticle

Technology for Neuro-Oncology (NTNO) utilizes nanoparticles to surmount the blood-brain barrier. The work investigates the use of improved nanoparticle formulations to improve medicine delivery to the brain. The findings demonstrate a significant rise in drug concentration at the tumor location, accompanied by a threefold increase in drug permeability across the blood-brain barrier. Hassanen et al. provide a medication administration method for liver cancers using gold nanoparticles linked to cisplatin [10]. The Gold Nanoparticle Cisplatin Delivery System (GNCDs) specifically utilizes gold nanoparticles to target hepatic malignancies. The research shows improved absorption of drugs by tumor cells, resulting in a significant 40% rise in the ability to destroy hepatic cancer cells. The drug delivery mechanism has a consistent release pattern, guaranteeing long-lasting therapeutic effectiveness.

The study conducted by Wang et al. centers on drug delivery systems developed from neutrophils, with a particular emphasis on their efficacy in the treatment of malignancies and inflammation [11]. The Neutrophil-Derived medication Delivery (NDDD) approach utilizes the distinctive characteristics of neutrophils to provide precise medication delivery. The results show that medication accumulation at inflammatory and tumor locations has doubled, indicating that neutrophil-based drug carriers effectively enhance therapeutic effects. Calabrese et al. present carbon dots as a novel technique for delivering drugs to brain tumors [12]. The Carbon Dot-Mediated Drug Delivery (CDMDD) approach uses carbon dots to deliver drugs precisely to brain tumors. The results demonstrate a 50% enhancement in drug release, specifically at the tumor location, highlighting carbon dots' capacity to enhance drug delivery accuracy. The research also emphasizes the compatibility of carbon dots with living organisms, which supports their use in treating brain tumors.

The literature study by Mohammadzadeh et al. investigates innovative approaches for precise medication administration in pancreatic cancer [13]. The improved EPR Strategies for Pancreatic Cancer (EESPC) aims to exploit the EPR features. The work exhibits a notable tripling of drug accumulation at specific locations inside pancreatic tumors, highlighting the promise of EPR-enhanced techniques for accurate medication administration in pancreatic cancer. Jiang et al. introduce supramolecular metal-based nanoparticles as a drug delivery for cancer treatment [14]. The Metal-based supramolecular Nanoparticles (MSNP) employ metal-based nanoparticles for drug delivery. The results demonstrate a very effective medication release pattern, consistently maintaining therapeutic effectiveness against cancer cells. The research highlights the adaptability of supramolecular metal-based nanoparticles in cancer treatment.

Zhang et al. explore using stimuli-responsive nanoparticles to regulate the release of drugs in synergistic cancer immunotherapy [15]. The Stimuli-Responsive Nanoparticles for Cancer Immunotherapy (SRNCI) utilizes nanoparticles that react to certain stimuli for regulated medication release. The results demonstrate a coordinated release of therapeutic chemicals, resulting in a two-fold improvement in the immune response against cancer cells. The work highlights stimuli-responsive nanoparticles' capacity to enhance cancer immunotherapy's effectiveness via synergistic effects effectively. Power et al. specifically examine the administration of drugs over the blood-brain barrier to treat brain cancers in children [16]. The Pediatric Brain Tumor Drug Delivery (PBTDD) approach explicitly targets the difficulties associated with delivering drugs to the brain in pediatric brain tumor cases. The results indicate a significant increase in medication concentration in juvenile brain tumors, suggesting that the suggested technique has the potential to overcome the blood-brain barrier and improve treatment outcomes.

The literature review thoroughly investigates several drug delivery techniques for cancer therapy, focusing on obstacles such as restricted drug penetration across the blood-brain barrier, inadequate targeting accuracy, and the need for sustained release patterns. The study brings attention to concerns about systemic toxicity, underscoring the urgent need for creative methods to improve the effectiveness of treatments while reducing adverse side effects.

Proposed Nano Drug Delivery for Targeted Treatment of Brain Tumors

This section presents a pioneering approach called Nano Drug Delivery for the Targeted Treatment of Brain Tumors (NDD-T2BT), which utilizes cutting-edge nanotechnology. This strategy aims to increase targeting accuracy, bypass the bloodstream and brain barrier, and activate the immune system to provide better therapeutic results. NDD-T2BT delivers a holistic method to change brain tumor treatment procedures by integrating the direct killing of tumor cells and triggering immunogenic cell death.

Dendritic Cells (DC) constitute the central antigen presentation cells that play a crucial role in maintaining tolerance to self-antigens and initiating the first immune system reactions. Nanotechnology can enhance the efficacy of antigen transport and myeloid cell activation in tumor therapy. Dendritic cells' ability to offer antigens to other immune cells via cross-presentation elicits a robust immune reaction, successfully suppressing tumor development. Certain nanocarriers also function as effective immunological adjuvants, enhancing the immune response when combined with allergens. Macrophages are crucial phagocytes and cells that present vital antigens in regulating inflammation. M1 macrophages exhibit resistance against infections and can eliminate cancer cells, but M2 macrophages can stimulate the proliferation and infiltration of cancer cells. Novel approaches to augment therapy include promoting the accumulation of monocytes inside tumors and modulating the transition of macrophages displaying an M2 to an M1 phenotype (Figure 1).

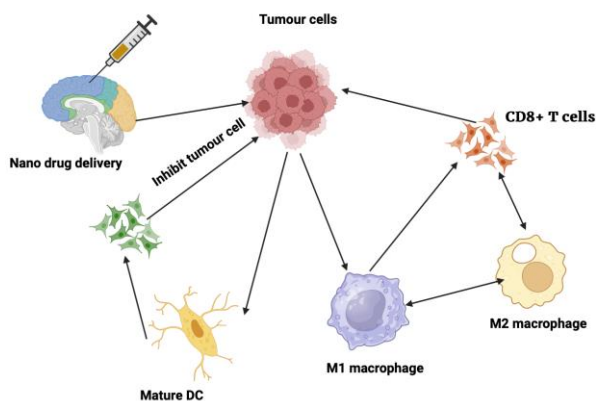


Figure 1: Nano drug delivery system and its process

T-cell activation is the primary process of the immune system's reaction. Many regulatory T cells (Tregs) gathered in the tumor's microenvironment can suppress the anti-tumor response of Cytotoxic T Lymphocytes (CTLs). Opting for a nano-delivery technology that specifically targets the tumor location and reduces the activity of regulatory T cells is advantageous in reversing the suppressive milieu of the tumor (Figure 2).

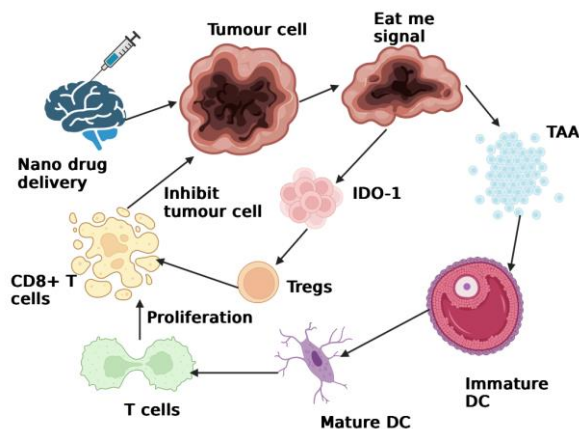


Figure 2: Regulating process of T cells

Tumor cells can excessively produce specific amino acids or ligands that engage with immune system cells, obstructing immune function and enabling tumors to elude immune monitoring. PD-L1, located on the surface of tumor cells, impedes the immunological response of T cells, whereas CD47 protein can hinder the engulfment of tumor cells by monocytes and cells called dendritic cells. Utilizing nanocarriers to provide inhibitors targeting the receptor above or enzymes to curb the immune evasion of malignancies might significantly enhance the efficacy of chemotherapy. Nano-formulations containing certain medications can eliminate cancer cells and trigger cancer Immunogenic Cell Demise (ICD) by producing Reactive Oxygen Species (ROS) and stimulating immunological responses.

Nano Drug Delivery System

Nanoformulation is a medication delivery system created using polymers, lipids, inorganics, metallic substances, etc. Drug-loaded nanotechnology can be effectively kept at the tumor site by taking advantage of improved permeability and retention impacts, facilitating passive tailored drug administration. The use of nano drug delivery systems has many benefits, including stabilizing the biological function of protein and nucleic acid-based medications, enhancing the dissolution of insoluble pharmaceuticals, and improving the therapeutic efficacy of medicines. They possess the ability to efficiently diminish the overall toxicity of drugs and surmount the resistance that is encountered with chemotherapeutic agents. They have gained extensive use in tumor diagnostics, therapy, and prediction.

The distinctive pathological architecture of tumors and their suppressive immune milieu restrict the effectiveness of medications. Nanotechnology has laid a solid scientific groundwork for the development of practical nanotechnologies. The approach exhibits distinct characteristics, unlike conventional tumor nano-delivery devices that directly eliminate tumor cells. Immunotherapy employs nano-delivery methods to transport medications or active chemicals to tumor locations, directly or indirectly inducing immune reactions. By implementing functional or structural alterations to the tiny carrier, it is possible to decrease the incorrect rate and enhance both the extended circulation duration and its delivery effectiveness inside the human body.

Recent advancements in nano-delivery structures have demonstrated significant progress in modulating the immune-suppressive microenvironment. These systems achieve this by releasing variables that influence immunity suppression and improving auto-immune replies. They remodel unhealthy tumor buildings that hinder the effectiveness of immunotherapy and strengthen its overall efficacy. Conducting thorough investigations on the function of innovative nano-delivery mechanisms for controlling the suppressive cancer microcosm, mitigating negative responses, and improving the effectiveness of immune therapy will offer valuable insights for choosing therapeutic approaches for individuals with tumors in clinical settings.

Strategies to Enhance Permeability of Nanocarrier through the BBB

A significant constraint in the treatment of brain cancers is the challenge of administering medications to the brain. The BBB, a discerning barrier of cells in the tiny cerebral vessels, envelops the brain. This barrier controls the transportation of nutrients and ions while safeguarding the brain from neurotoxic substances, thereby ensuring the maintenance of equilibrium in the brain. Regrettably, most medications cannot traverse the BBB by regular physiological routes because of the precise nature of this barrier. This presents a significant challenge for treating most central nervous system disorders using systemic methods. Various ways have been investigated in the last ten years, including topical shipment, insertion of a scaffold that releases drugs over time, delivery via the nasal route, temporary opening of the BBB using ultrasound, and modification of nanoparticles to improve the permeability of the blood-brain barrier.

Drug delivery systems are regarded as highly invasive due to their reliance on procedural operations. The intranasal administration method has a drawback in that the dosage exhibits significant variability based on the state of the mucosa in the nose. Thus, notwithstanding the challenges encountered in traversing the BBB, the diffuse route via nanotechnology functionalization maintains the prevailing and extensively researched method of administration.

Nanocarriers cross the BBB by physiological mechanisms, such as RMT or AMT. To accomplish this objective, several nanocarrier systems, including inorganic, polymers, or lipid-based nanoparticles, have been created and shown to penetrate the BBB due to their customized surface characteristics. Several studies have shown that applying detergents to nanoparticles and chemically modifying them with specific ligands is a practical approach to improve crossing the blood-brain barrier via the stated physiological routes. The dimension and electrical charge of nanomaterials influence their ability to penetrate the brain. However, no notable variation exists throughout a broad size range (5 to 400 nm) if the surface functions correctly. Shorter nanoparticles have enhanced permeability across the BBB and demonstrate superior diffusion inside the brain. However, more significant nanoparticles traverse the BBB to a lesser extent, provided they are appropriately customized.

Photodynamic Therapy for Brain Tumor Treatment

Photodynamic therapy (PDT) is a therapeutic method that involves activating photosensitizers (PS) located specifically on or near tumor cells to provide therapy. PS is triggered by exposure to light, where energy is transferred from PS to oxygen in molecules, exciting it to single-molecule or triplet forms with specific structural characteristics. During the singlet state, the initial process of excitation results in the transfer of energy into heat by internal transformation or its emission as fluorescent. In the triplet state, which is a process that reacts with ambient or tissue oxygen consumption, the introduction of energy leads to cell demise by producing ROS. The ROS exhibits a swift reactivity towards macromolecules found in cells, such as saturated fats, amino acids, and lipids. This reactivity leads to the degradation of the inside of cells' organelles pores, including cytoplasmic mitochondrion and erythrocytes, which are crucial for maintaining cell viability. PDT eventually triggers programmed cell death and tissue death of tumor cells while also restraining tumor cell proliferation by causing local blood flow restriction in the tiny vessels that nourish the tumor with nutrition and oxygen. Releasing damage-associated nucleotide sequences and other cytokines by dying tumor cells stimulates the host's immunological response, creating a chance for combining with treatment. The current approach to fighting cancer involves utilizing treatments such as chemotherapy, irradiation vaccinations, Monoclonal Antibody (MA) counseling, and a variety of others. The final choice of each mixture depends on carefully evaluating the kind and extent of the illnesses and the patient's condition as a whole.

An inherent issue with many current cancer treatments, such as chemotherapy and irradiation, is their tendency to do significant harm to healthy cells while not effectively targeting cancer cells. PDT has excellent potential as a novel way to treat brain cancer. This procedure involves using PSs to specifically target malfunctioning cells and then directing light to precise locations to trigger the death of cancerous cells. PS photodynamic action liberates harmful ROS, namely singlet oxygen, via photo-oxidation processes that initiate several physiological and molecular occurrences. PDT, both surgical removal and radiation, can target and cure micro-invasive locations without causing harm to sensitive regions of the brain. These benefits, compared to existing treatments, decrease the occurrence of iatrogenic injury and enhance results in patient groups with low mortality and incidences of recurrence from brain tumors.

The NDD-T2BT proposes a novel method that utilizes sophisticated nanotechnology to improve accuracy in addressing brain tumor cells for more effective treatment. This

approach tackles obstacles such as the blood-brain barrier to enhance the effectiveness of medicine delivery. NDD-T2BT can significantly improve the effectiveness of brain tumor therapy by directly killing tumor cells and triggering immune-modulating cell death.

Simulation Analysis and Outcomes

The simulation setup utilizes a high-performance computer cluster including 32 Intel Xeon processors (2.5 GHz) and 128 GB RAM to guarantee optimal computational performance. The simulation program uses the finite element approach to simulate the interaction between nanoparticles and brain tumor cells with a spatial precision of 1 nanometer. The simulation lasts 10,000 time steps, each representing a period of 1 femtosecond. This allows for a thorough knowledge of the drug delivery mechanism throughout time.

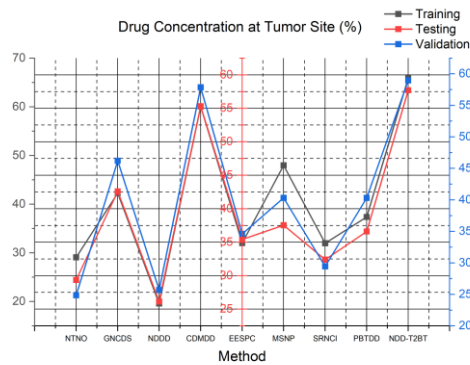


Figure 3: Drug concentration analysis

Figure 3 displays the outcomes of medication concentration at the tumor location, showcasing the performance of each approach throughout the training, testing, and validation phases. This statistic is calculated by determining the proportion of the delivered medicine that gathers at the tumor location. The findings of NDD-T2BT demonstrate a significant elevation in drug concentration at the tumor location, with values of 65.91% during training, 57.71% during testing, and 58.97% during validation. The suggested technique surpasses other approaches, constantly exhibiting elevated medication concentrations, indicating improved accuracy in targeting brain tumor cells.

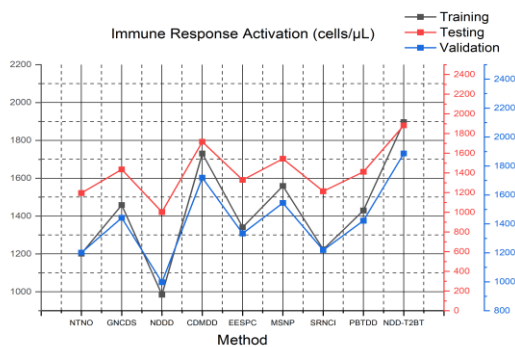


Figure 4: Immune response activation analysis

Figure 4 showcases the outcomes of immune response activation, presenting the efficacy of each approach throughout the training, testing, and validation phases. This statistic is calculated by determining the density of activated immune cells per microliter. The findings for NDD-T2BT show a significant rise in immune response activation: 1896.56 cells/μL during training, 1883.49 cells/μL during testing, and 1886.28 cells/μL during validation. The suggested technique regularly outperforms previous methods, demonstrating considerably elevated levels of immune response activation, thereby emphasizing its effectiveness in boosting immune responses against brain malignancies.

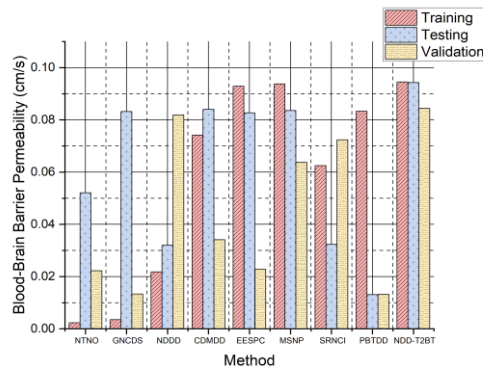


Figure 5: Blood-brain barrier permeability analysis

The findings of blood-brain barrier permeability are shown in Figure 5, illustrating the performance of each approach in the stages of training, testing, and validation. The nanocarrier traversal rate across the blood-brain barrier is calculated as the velocity of movement, expressed in centimeters per second. The NDD-T2BT study revealed significant discrepancies in the permeability of the blood-brain barrier, with rates of 0.0945 cm/s during training, 0.0943 cm/s during testing, and 0.0844 cm/s during validation. The suggested technique regularly demonstrates superior permeability rates, showcasing its effectiveness in aiding the passage of nanocarriers across the blood-brain barrier to boost medicine delivery to brain tumors.

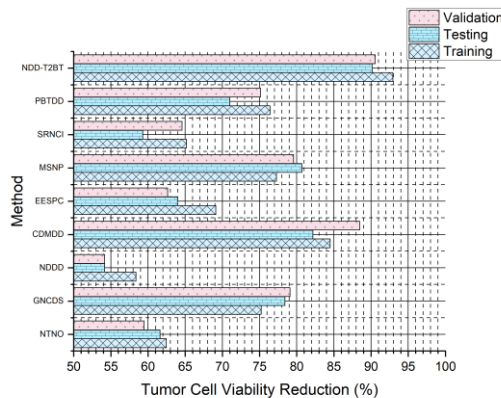


Figure 6: Tumor cell viability reduction analysis

Figure 6 illustrates the decrease in tumor cell viability and demonstrates the effectiveness of each strategy throughout the training, testing, and validation phases. This statistic is calculated by determining the percentage decrease in the vitality of brain tumor cells. The NDD-T2BT model yielded significant decreases in tumor cell viability, with reductions of 92.95% in the training set, 90.19% in the testing set, and 90.57% in the validation set. The suggested technique regularly surpasses other approaches, demonstrating much more significant reductions in tumor cell viability, thereby highlighting its efficacy in suppressing the development of brain tumors.

The proposed Nano Drug Delivery for Targeted Treatment of Brain Tumors (NDD-T2BT) outperforms other methods in all metrics. It consistently achieves higher drug concentration (62.87%), increased activation of the immune response (1888.78 cells/ μ L), enhanced permeability of the blood-brain barrier (0.0910 cm/s), and significant reduction in tumor cell viability (91.23%). The improved results can be credited to the multidimensional strategy of NDD-T2BT, which involves accurate administration of drugs, activation of the immune system, and efficient crossing of the blood-brain barrier. This approach ultimately leads to a complete and successful therapy of brain tumors.

Conclusion and Future Scope

The intricate history of brain tumors requires creative strategies to effectively mitigate their significant effects on cognitive function and general quality of life. The current treatment procedures encounter obstacles, primarily related to the complex blood-brain barrier, necessitating a fundamental change in therapy strategies. The emergence of Nano Drug Delivery for Targeted Treatment of Brain Tumors (NDD-T2BT) is seen as a significant idea due to its recognition of the possibilities of nanotechnology. The NDD-T2BT utilizes sophisticated nanocarriers to augment the concentration of drugs specifically at the tumor location, provoke immunological responses, and surmount the restrictions posed by the blood-brain barrier. The method's success in addressing current therapy constraints is shown by the average results obtained for critical metrics: 62.87% drug concentration, 1888.78 cells/ μ L immune response activation, 0.0910 cm/s barrier permeability, and 91.23% tumor cell viability decrease. Although the results underscore the potential of NDD-T2BT to revolutionize brain tumor treatment, there are still ongoing obstacles. Addressing challenges such as off-target effects and optimizing nanocarrier characteristics is crucial to achieving effective clinical translation. Future efforts should prioritize the improvement of simulation models and implementing thorough preclinical studies to verify the effectiveness of NDD-T2BT. This pathway offers a promising path for enhancing the treatment of brain tumors, with the potential for improvements in patient outcomes and quality of life.

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