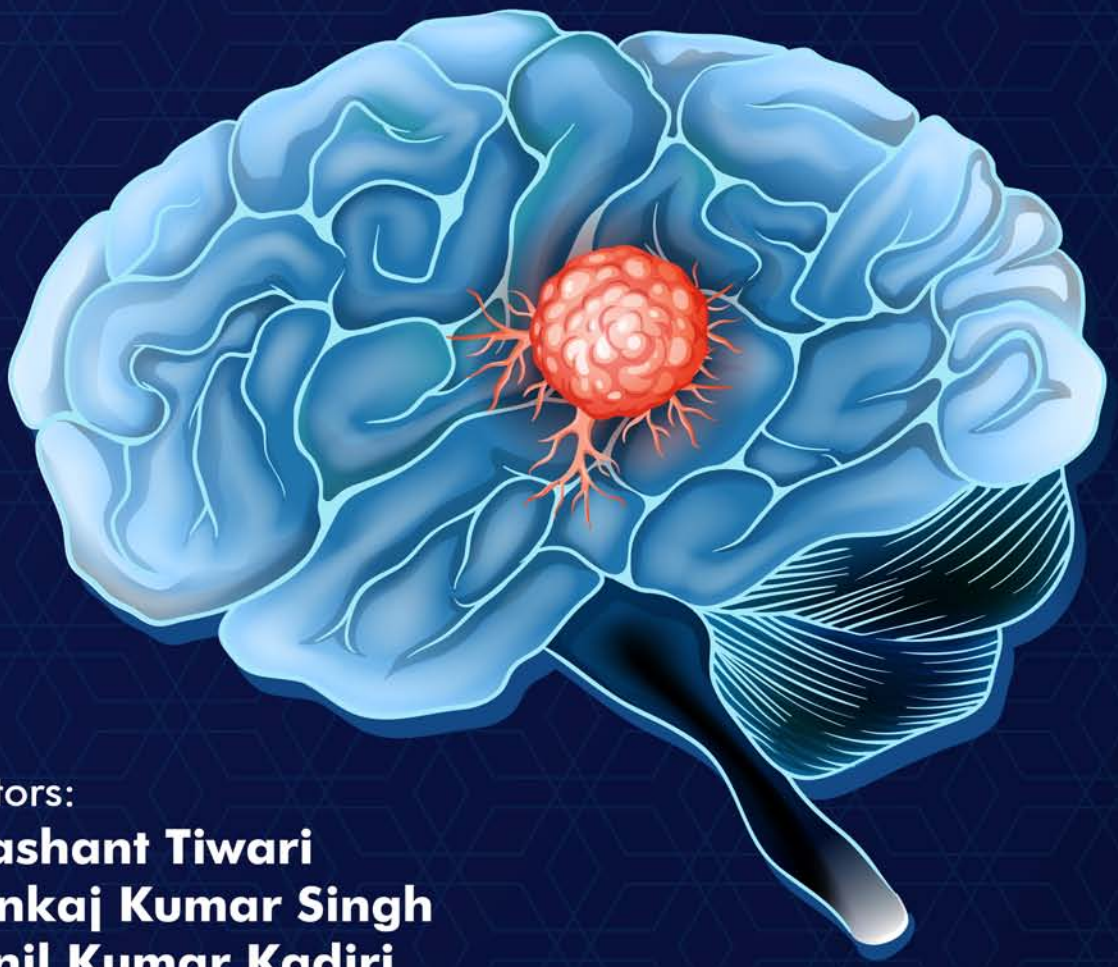
BRAIN TUMOR DRUG DEVELOPMENT

CURRENT ADVANCES AND STRATEGIES | PART 2



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Brain Tumor Drug Development: Current Advances and Strategies

(Part 2)

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Brain Tumor Drug Development: Current Advances and Strategies *(Part 2)*

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FOREWORD

In recent years, brain tumor research has made remarkable strides, bringing to light new pathways, mechanisms, and potential therapeutic strategies. However, the complexity of the brain and the heterogeneity of brain tumors, particularly glioblastomas, continue to present formidable challenges in developing effective treatments. Against this backdrop, the book "Brain Tumor Drug Development: Current Advances and Strategies," edited by Dr. Prashant Tiwari, Dr. Pankaj Kumar Singh, and Dr. Sunil Kumar Kadiri, emerges as a critical resource for both experienced researchers and new entrants into the field.

The editors, each with extensive expertise in oncology, pharmacology, and drug development, have compiled a remarkable collection of insights that encompass the full spectrum of current advances in brain tumor therapeutics. From the latest molecular and genomic approaches to emerging targeted therapies, this book encapsulates a dynamic and evolving landscape. The emphasis on precision medicine, immunotherapy, and the repurposing of existing drugs highlights the cutting-edge strategies that are driving the next generation of brain tumor treatments.

In particular, the book addresses some of the most pressing questions facing the field: How can we overcome the blood-brain barrier to deliver effective drugs? What role do molecular biomarkers play in predicting patient outcomes? And how can we harness the immune system to combat tumors that have historically been resistant to conventional treatments?

The editors have ensured that this book not only reflects the state-of-the-art in brain tumor drug development but also points toward the future. By exploring the potential of novel therapeutic agents, innovative delivery systems, and combination treatments, this book provides readers with a comprehensive understanding of the strategies that are being employed to tackle one of the most aggressive forms of cancer.

I hope that this book will inspire and inform the next wave of discoveries, bridging the gap between fundamental research and clinical application. Whether you are a researcher, clinician, or industry professional, Brain Tumor Drug Development: Current Advances and Strategies is an invaluable resource that provides both a broad overview and in-depth discussions of the ongoing efforts to develop effective therapies for brain tumors.

I congratulate the editors and contributors for compiling such a timely and impactful book, and I am confident that it will make a lasting contribution to the field of brain tumor research.

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PREFACE

Brain tumors, particularly malignant forms such as glioblastoma multiforme, present formidable challenges in oncology due to their aggressive nature, complex biology, and resistance to conventional therapies. Despite progress in surgical resection, radiotherapy, and chemotherapy, survival rates remain dismal, underscoring the urgent need for innovative drug development strategies. This book addresses the evolving landscape of brain tumor therapeutics, focusing on molecularly targeted agents, immunotherapies, and advanced delivery systems designed to overcome the limitations posed by the blood-brain barrier and tumor heterogeneity.

Recent advances in genomics and proteomics have enabled the identification of actionable molecular targets, such as EGFR amplification, IDH mutations, and MGMT methylation status, which inform the development of personalized treatment regimens. Immunotherapeutic approaches, including checkpoint inhibitors, CAR-T cell therapy, and tumor vaccines, are gaining traction for their potential to harness the immune system against brain tumors. Furthermore, nanotechnology-based drug delivery platforms and focused ultrasound techniques are being explored to enhance therapeutic penetration and precision within the central nervous system.

This compilation brings together contributions from leading researchers, clinicians, and regulatory experts to provide a comprehensive overview of current strategies and future directions in brain tumor drug development. It emphasizes translational research, adaptive clinical trial designs, and the integration of real-world evidence to accelerate the bench-to-bedside transition. The role of pharmacogenomics, biomarker-driven therapy, and combination regimens is also discussed, offering insights into optimizing efficacy while minimizing toxicity.

As the field advances, interdisciplinary collaboration and regulatory harmonization will be essential to translate scientific discoveries into clinically meaningful outcomes. This book aims to serve as a valuable resource for academic investigators, pharmaceutical developers, and healthcare professionals committed to improving the prognosis and quality of life for patients with brain tumors. Through continued innovation and strategic integration of emerging technologies, the future of neuro-oncology holds promise for more effective and personalized therapeutic solutions.

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CHAPTER 1

Phytopharmaceuticals for Brain Tumor: Opportunities and Challenges

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Abstract: Phytochemicals from plants have provided humans with numerous health benefits. Still, the special properties of the BBB (Blood-Brain Barrier) impede their access to the targeted tissue, and therefore, prevent their therapeutic use in treating brain disorders. In response to the increasing number of fatal diseases, scientists and medical experts have created strict new therapies. The concerning rise in the incidence of fatal neurodegenerative illnesses has brought attention to the need for efficient treatment alternatives. However, the conventional medications that are used to treat them already have disadvantages that make them less than optimal. The most sought-after alternative to traditional medications is now traditional herbal remedies, which try to offset the disadvantages of synthetic treatments. Their accessibility, cost, and, most of all, their safety and effectiveness have had a major impact on their success against some of the most serious kinds of neurological illness as well as consumer dependence. Clinical and laboratory data indicate that they offer the potential to treat stroke, Alzheimer's, Parkinson's, and other illnesses. For the treatment of neurological illnesses, researchers are considering nanosystems based on herbs to enhance the transport and bioavailability of phytochemical compounds. Neurodegenerative diseases are the primary research targets for this investigation into polyherbalism, herbal-medicinal drugs, and herbal-based nanosystems. This chapter explores phytochemicals and their potential medicinal uses.

Keywords: Brain tumor, BBB, Bioactive, Nano-delivery, Nanosystem, Phytopharmaceuticals.

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INTRODUCTION

Modern medicine would not exist without the use of natural phytochemicals, which have contributed to the development of well-known medicinal compounds. Various naturally occurring compounds derived from plants are collectively known as phytochemicals. The medicinal benefits of plants were first recognized by humans *via* their deliberate or accidental usage, leading to the advancement of medical science over herbology [1]. Modern pharmaceutical engineers have successfully utilized compounds derived from plants in the development of medications. The usual process begins with the isolation and purification of target phytochemicals. Then, their pharmacological capabilities and pharmacodynamics are evaluated in the lab, culminating in a druggability evaluation and the initiation of their development. To make them more effective, certain phytochemicals are derivatized or undergo structural optimization [2].

Using phytochemicals, a small-molecule library was also created for computer-based virtual drug screening and high-throughput drug screening. They offer new possibilities for pharmacological research and library enhancement due to their highly complex architectures [3]. Furthermore, significant study areas in current organic chemistry include obtaining precursors that can be derivatized in various ways, reducing synthesis costs, increasing yield and purity, and fully synthesizing naturally occurring phytochemicals of great economic value. Medications derived from plants can reach the human body through various pathways. Nasal feeding, oral delivery, and intravenous injection are the primary modalities of administration currently used [4, 5].

Because many phytochemicals exhibit pharmacological properties in food, they can be taken orally and have excellent intestinal absorption and tolerance to stomach acid. The low bioavailability of orally administered phytochemicals is attributed to the Blood-Brain Barrier (BBB) and limited targeted organ accumulation [6]. Since the direct therapeutic effects of many phytochemical candidates were inadequate, they either remained in the laboratory or were developed into healthcare products. Although it is still limited to brain targeting, intravenous administration increases the concentration of medicine in the blood and reduces drug loss in the gastrointestinal system [7].

Brain disorders are not contagious but may run in families and are characterized by abnormalities in normal brain structure and function that arise from birth defects or genetic malfunctions. Several illnesses and disorders can affect the brain, including malformations, tumors, infections, and traumas [8]. The increasing prevalence of brain illnesses due to the world's aging population calls for immediate action in the form of improved diagnostic tools, effective

treatments, and effective prevention measures. The blood-brain barrier, a special capillary control system that keeps most substances from the outside world from entering the brain and spinal cord, has eluded researchers. Unlike other organs, the brain is not accessible *via* the circulatory system for over 98% of neurotherapeutic chemicals and more than 100% of larger therapeutic molecules [9].

Many innovative brain delivery platforms have emerged as a consequence of nanomedicine's rapid development; some have even received regulatory approval after demonstrating encouraging results in animal studies. In addition, research on nasal delivery as a means to enhance drug absorption in the brain is ongoing [10]. The use of lipid-soluble solvents in combination with nasal administration of certain medication formulations has the potential to reduce drug loss in blood circulation and improve medicine uptake by the brain *via* the olfactory bulb. Unfortunately, many drugs still don't work on humans because our olfactory bulbs are much smaller than those of mice, in comparison to the brain. Nanodelivery formulations may also improve BBB translocation efficiency after nasogastric injection [11].

Despite the widespread recognition of phytochemicals as potential therapeutic agents, there is a limited understanding of the molecular mechanisms by which these substances exert their effects. Unlike healthcare commodities, clinical medications require precise dosing, clear indications, and a comprehensive understanding of their metabolic and pathological interactions. Further study on its working mechanisms, particularly in conjunction with computational drug design and structural biology, may lead to the identification of additional potential *de novo* candidates derived from phytochemicals [12].

Nanocarriers (NCs) may enter the majority of cells by endocytosis and transcytosis, as determined by the research study. There has been a lot of focus lately on the use of NCs for administering drugs to the brain. To facilitate better BBB crossing, drugs were formerly combined with surfactants and co-solvents such as ethyl alcohol, polysorbate 80, dimethyl sulfoxide, and so on [13]. Nonetheless, these substances seriously jeopardize the BBB's integrity and defensive activities. The unique qualities of NCs, including low toxicity, selectivity, biocompatibility, small size, and solubility, combined with their ease of transport across the BBB, have made them a promising therapeutic option for brain diseases and disorders [14]. However, the therapeutic efficiency of conventional drugs used to treat brain disorders is limited due to their low absorption in brain tissue and several serious side effects on healthy tissue. The secondary metabolites of plants that have garnered recent attention include phytochemicals and phytonutrients. This covers substances such as phenolic

CHAPTER 2

Current Innovation in *In Vitro*, *Ex Vivo* and *In Vivo* Screening of Brain Cancer

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Abstract: In recent years, brain tumors have become one of the leading causes of cancer-related mortality in children. Among all brain cancers, glioblastoma (GBM) is considered one of the most aggressive and lethal malignancies in oncology. The difficulty in replicating the complex structure of the brain and its surrounding microenvironment is a major obstacle to understanding potential therapeutic methods for this condition. To overcome the challenges of treating brain tumors, researchers have focused on studying different models of brain tumors. These models offer valuable insights that can aid scientists in developing more effective treatments for brain tumors. *In vitro*, tumor models are essential for understanding the molecular and cellular mechanisms underlying the malignant progression of tumor blood vessels. *Ex vivo* tumor models involve the study of malignant tissues removed from living organisms in a controlled laboratory environment. These models utilize tissue slices, organoids, and brain tumor cell cultures. Furthermore, *in vivo* models can be useful for preclinical testing of potential new treatment approaches and for investigating the molecular mechanisms of brain tumors and their associated microenvironments. However, this chapter discusses brain cancer, including its types, symptoms, and diagnostic characteristics. It explains the differences in cell-signaling mechanisms between glial and non-glial brain cancers. The chapter also covers the latest advancements in the prognosis of GBM. Additionally, it includes a discussion of different types of pre-clinical models used to overcome the limitations of current therapeutic approaches, such as *in vitro* 2D and 3D cellular models. Furthermore, the chapter addresses *in vivo* animal models of brain cancer created through chemical and genetic methods, as well as *ex vivo* models like patient-derived models, xenografts, and organoids.

Keywords: Brain tumor, *In vitro* models, *In vivo* models, Signaling pathways.

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INTRODUCTION

Brain tumors represent a broad and diverse category of cancers that affect the central nervous system [1]. Among these, glioblastoma (GBM) is considered one of the most aggressive and lethal primary brain malignancies in oncology. The patients show a terrible prognosis and exhibit a poor quality of life as the disease progresses [2]. GBM has been stated as grade IV gliomas by the World Health Organization (WHO), displaying a 5-year survival of 7.2%. It often affects the cerebral hemispheres, with a peak incidence between 45 and 70 years old. It has a high genetic heterogeneity and an infiltrative nature. The protective presence of the blood-brain barrier has hugely contributed to the worsened treatment efficacy [3]. The current standard of care for brain tumors—primarily involving surgical resection followed by prolonged chemotherapy—offers limited improvement in patient survival. Despite advancements in neurosurgical techniques, radiation therapy, and chemotherapeutic regimens, the prognosis for patients with high-grade gliomas, particularly glioblastoma multiforme (GBM), remains dismal. GBM's highly proliferative and infiltrative nature poses a significant challenge, as complete surgical eradication is virtually impossible. This biological aggressiveness renders conventional therapeutic approaches largely ineffective [4]. Modern cancer diagnosis increasingly relies on genomic, molecular, and histopathological analyses, which provide critical insights into tumor classification and guide personalized treatment strategies [5]. To address the limitations of existing therapies, researchers have developed various 2D and 3D *in vitro* models. Among these, three-dimensional models offer superior regulation of cell morphology, and enable advanced techniques such as live imaging and antibody staining, making them particularly valuable for preclinical research [4]. Additionally, *ex vivo* and *in vivo* models are widely employed to investigate tumor angiogenesis, growth kinetics, and therapeutic responses, offering translational relevance in understanding tumor biology and evaluating novel interventions [6]. This book chapter provides a comprehensive overview of brain cancer subtypes, associated clinical symptoms, and diagnostic features. It aims to enhance readers' understanding of the cell-signaling pathways involved in both glial and non-glial brain tumors, thereby laying the foundation for exploring emerging therapeutic strategies and precision oncology approaches.

Recent advancements in the prognosis of glioblastoma (GBM) will also be discussed. In addition, various two-dimensional (2D) and three-dimensional (3D) *in vitro* cellular preclinical models that address the limitations of current treatment modalities are reviewed. *ex vivo* models, such as patient-derived xenografts and organoids, along with chemically and genetically induced *in vivo* animal models of brain cancer, are also examined.

BRAIN CANCER- CLASSIFICATIONS, SYMPTOMS, AND DIAGNOSIS

Classification

Brain tumors are broadly classified into two categories: malignant and benign. Malignant tumors consist of cancerous cells that can infiltrate adjacent tissues and, in some cases, metastasize to distant organs. In contrast, benign tumors typically exhibit slow growth, are less invasive, and have a lower likelihood of recurrence following treatment. Tumors are further categorized based on their origin: Primary brain tumors originate within the brain or Central Nervous System (CNS). Secondary brain tumors, or brain metastases, result from the spread of cancer from other parts of the body to the brain [7 - 9]. The World Health Organization (WHO) classifies brain tumors using a grading system that reflects their biological behavior and aggressiveness: Grade I tumors are generally benign, slow-growing, and most commonly observed in pediatric populations. These tumors are often curable with surgical resection. Grade II tumors, more prevalent in adults, include oligodendrogliomas, oligoastrocytomas, and astrocytomas. They are low-grade gliomas with a potential for progression. Grade III tumors, such as anaplastic oligodendrogliomas, anaplastic oligoastrocytomas, and anaplastic astrocytomas, exhibit greater cellular atypia and invasiveness than Grade II tumors. Grade IV tumors, notably glioblastoma multiforme (GBM), represent the most aggressive form of glioma, characterized by rapid proliferation, extensive infiltration, and poor prognosis. High-grade gliomas encompass Grade III and IV tumors, which are malignant and challenging to surgically remove due to their diffuse invasion into surrounding brain tissue. In contrast, low-grade gliomas include Grade I and II tumors, which are typically benign and may be amenable to complete surgical excision [10].

Symptoms

In addition to being a typical sign of disease, headaches may also be an indication of a brain tumor. Roaring or quivering muscles in the limbs are symptoms of seizures, which may affect as many as 80% of patients with brain tumors. It is unusual to feel unwell, particularly when you are moving abruptly. An increase in intracranial pressure may affect the brain, leading to drowsiness or unconsciousness. Vision loss, floating objects, or tunnel vision might result from worsening eye conditions. Confusion, short-term memory loss, and abnormal thought processes could result from changes in behavior & personality, and leakage of milk from the breasts are some of the clinical manifestations involving brain tumors [8, 11, 12].

CHAPTER 3

Natural Bioactive Acting on Brain Tumor Microenvironment

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Abstract: The brain tumor microenvironment (TME) is a complex and dynamic niche composed of tumor cells, immune cells, blood vessels, extracellular matrix (ECM), and signaling molecules that interact to support tumor progression, angiogenesis, and immune evasion. Targeting the TME has emerged as a promising strategy for combating brain tumors, particularly gliomas, which remain challenging to treat with conventional therapies. In this context, natural bioactive compounds have gained significant attention due to their multi-targeting abilities, biocompatibility, and reduced side effects compared to synthetic drugs. These abstract reviews key natural bioactive compounds that modulate the brain tumor microenvironment, focusing on their mechanisms of action and potential therapeutic benefits. The potential for modulating the microenvironment of brain tumors has been highlighted by recent studies on natural bioactives, which are compounds found in plants, fungi, and marine organisms. These bioactives can influence key pathways involved in tumor growth, immune evasion, angiogenesis, and metastasis. This review focuses on the mechanisms by which natural bioactives, such as curcumin, resveratrol, epigallocatechin gallate (EGCG), and cannabinoids, exert their effects on the brain tumor microenvironment. It has been demonstrated that these compounds inhibit tumor growth by modulating oxidative stress, inflammation, and signaling pathways, including MAPK, PI3K, and NF-κB. Additionally, the review discusses the challenges and future directions in translating these findings from preclinical models to clinical applications. Bioactives and their interactions with the brain tumor microenvironment provide the basis for developing new therapeutic strategies which can improve patient outcomes and reduce the side effects associated with standard treatment.

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Keywords: Brain tumor, Curcumin, Cannabinoids, EGCG, Inflammation, Microenvironment, Natural bioactive, Oxidative stress, Resveratrol, Signaling pathways.

INTRODUCTION

Brain tumors, encompassing both primary and metastatic neoplasms, present significant therapeutic challenges due to their intricate and resilient microenvironment. A diverse mixture of immune cells, stromal cells, tumor cells, and extracellular matrix constituents comprises the tumor microenvironment. It contributes greatly to tumor progression, therapeutic resistance, and poor prognoses. Conventional treatment modalities, including surgery, radiation, and chemotherapy, often fall short due to the tumor's adaptive mechanisms and the protective nature of the Blood-Brain Barrier (BBB). Recent advances in cancer research have shifted focus towards the potential use of natural bioactive compounds—substances derived from plants, fungi, and marine organisms—as therapeutic agents [1]. These compounds, known for their diverse pharmacological properties, offer a promising avenue for targeting the brain tumor microenvironment. Unlike synthetic drugs, natural bioactives often possess multi-targeted mechanisms of action, enabling them to modulate various signaling pathways simultaneously. Tumour cells, stromal cells, immune cells, and extracellular matrix constituents make up the diverse mixture that is the tumour microenvironment [2]. There are a number of natural bioactives that have garnered a considerable amount of interest, including curcumin, resveratrol, epigallocatechin gallate (EGCG), and cannabinoids. Tumorigenesis is influenced by oxidative stress, inflammation, angiogenesis, and cell proliferation, all of which are mediated by bioactive compounds [3]. Additionally, they have shown potential in modulating the immune response and enhancing the permeability of the BBB, thereby improving drug delivery to the tumor site [4].

KEY COMPONENTS OF THE BRAIN TUMOR MICROENVIRONMENT

Brain tumor microenvironments are highly complex and dynamic ecosystems that significantly influence tumor development, progression, and resistance to therapy. The development of effective therapeutic strategies requires a thorough understanding of its key components (Fig. **1**). The primary elements of the brain tumor microenvironment include:

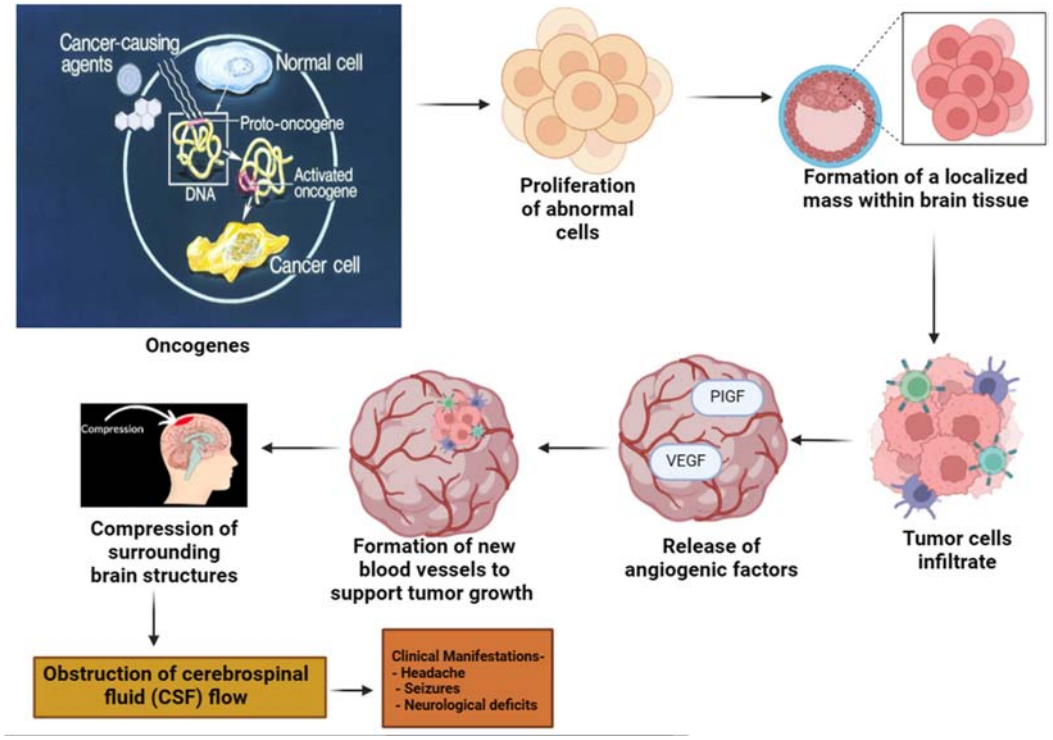

Fig. (1). Molecular pathology of progress of brain tumour for better understanding to develop effective therapeutic strategies.

Tumor Cells

Heterogeneity

Brain tumors, particularly gliomas, exhibit significant cellular heterogeneity, meaning they comprise diverse cell populations with varying genetic, molecular, and phenotypic characteristics. This heterogeneity contributes to the complexity and adaptability of the tumor, leading to varied responses to treatment and challenges in effectively targeting all tumor cells. It includes subpopulations such as cancer stem cells that possess high resistance to conventional therapies and are implicated in tumor recurrence. Treatment strategies for brain tumor patients must take into account and address this heterogeneity in order to be effective and personalized.

Stem-like Cells

Within brain tumors, there is a subpopulation of cells known as tumor-initiating cells or cancer stem cells that exhibit stem-like characteristics and possess the ability to differentiate and self-renew. These cells are highly resilient and often

CHAPTER 4

Advancements in Brain Tumor Treatment: Harnessing Nanotechnology for Promising Solutions

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Abstract: Brain tumors, including brain metastases and gliomas, are among the worst cancers in the world due to the ineffectiveness of existing treatment techniques. Currently, many treatments are used to relieve pain and prolong survival time, including chemotherapy, radiotherapy, and surgery, although all are destructive and prolong the patient's lifespan by more than one year, and relapse is common even after effective treatment. Numerous factors contribute to the failure of cancer treatments, including physiological barriers like the Blood-Brain Tumor Barrier (BTB) and the Blood Brain Barrier (BBB), which are difficult for existing macromolecularantitumor medications to cross. These failure factors, together with the long-term success of treatment, necessitate new developments in brain tumor treatments. Nanomedicine has emerged as one of the most promising options for advancing or improving brain tumor care. Targeted drug delivery with nanoparticles has the potential to significantly reduce dosage, improve release characteristics, increase specificity and bioavailability, lengthen the shelf life, and lessen toxicity and side effects. Some nanodrugs can cross the BBB and BTB, which are major impediments to treating brain cancers. In this chapter, we will examine the current state of the art, as well as the most unique and exceptional innovations in treatment options, including a concise summary of preclinical and clinical research on nanodrugs in brain tumor therapy.

Keywords: Brain tumor, Blood-brain barrier, Nanomedicine, Nanoparticles, Targeted drug delivery.

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INTRODUCTION

One of the most aggressive forms of cancer that has ever been identified is brain tumors. Even with improvements in modern therapeutic methods, these illnesses usually have disastrous consequences. The mechanism and properties of tumor cell development are extensively explored in the current research. A door to new treatments may be opened with the discovery of novel targets or drugs that work better than ones that already exist. A normal cell can become cancerous through a series of genetic changes that occur during the multistep process of cancer growth [1]. Six physiological factors have been found by Hanahan and Weinberg [2] to be capable of inducing cancer like self-sufficiency in generating signals for cell development, namely (i) resistance to cell proliferation inhibitors, (ii) insensitivity to inhibitors of cell proliferation, (iii) avoiding the processes of apoptosis, (iv) uncontrolled and unchecked replication/duplication process, (v) capacity to stimulate angiogenesis which support the tumor cell growth, and (vi) capacity to infiltrate biological materials. Two more characteristics were also identified in cancer development, including alterations in metabolic processes within the cell that may facilitate the formation of malignant cells and the capacity to evade the immunological reaction. By understanding the mechanisms underlying carcinogenesis, one can prevent the development of tumors that are linked to unchecked cellular replication brought on by either a decrease in tumor suppressor genes, which inhibit cancer cell proliferation, or an increase in protooncogenic factors, which promote normal cell proliferation.

Central Nervous System (CNS) malignancies sometimes exhibit significant histological variety. As a result, in 1957, the WHO proposed a tumor classification in order to harmonize detection and, eventually, develop a universal classification [3]. Based on the degree of Malignancy, the WHO currently divides brain tumors into four categories, Grades I to IV, as determined by histological analysis like cellular pleomorphism, endothelial hyperplasia, nuclear atypia, cell division activity, necrosis process, angiogenesis, tumor suppression gene factors, protooncogenic factors, clinical features of disease and responses to the medical treatments. The following are the four types of grades:

- Grade I, also known as pilocytic astrocytoma, is characterized by moderate growth, the absence of malignancy, and extended survival. It is treated surgically.
- Grade II, also known as low-grade astrocytoma, is characterized by relatively moderate growth; malignancy may be present or not, and recurrence often occurs when the tumor progresses to a higher grade.

- Grade III, also known as anaplastic astrocytoma, is characterized by malignant, a tendency to progress to a higher grade, and high mitotic activity. Most patients are treated with chemotherapy and radiotherapy.
- Grade IV, also known as glioblastoma mutiforme, is characterized by fast growth, aggressive malignancy, extensive necrosis, and a very low survival rate.

As per the Central Brain Tumor Registry of the United States (CBTRUS) reports from 2005 to 2009, 20.6 cases of CNS tumors were reported in the US for every 100,000 individuals annually, of which 7.3 cases had malignant tumors and 13.3 cases had low-grade tumors per 100,000 individuals [4]. 50% of the primary grade brain tumors convert into glioblastoma multiforme, and its 5-year survival rate is less than 10% [5].

The global survey, which included personal health data from 37.5 million cancer patients diagnosed between 2000 and 2014, revealed that overall cancer survival rates are increasing—particularly for highly malignant diseases [6]. Cancer is responsible for approximately one in every six deaths worldwide. According to Global Cancer Statistics 2020, 19.3 million new cancer cases resulted in 10 million deaths [7]. More than 70% of these deaths occur in low- and middle-income countries. In adults, brain metastases account for nearly 150,000 cases of intracranial malignancies in the United States alone. Between 8% and 10% of adult cancer patients develop brain metastases; however, the incidence varies significantly depending on the type of primary tumor. Approximately 70% of brain metastases originate from breast and lung cancers. Other cancers that may metastasize to the brain include colorectal, renal cell carcinoma, and melanoma [8, 9].

Glioblastoma and other high-grade brain tumors are often fatal due to their resistance to radiation and chemotherapy, as well as their highly invasive nature [10]. The most common malignant brain tumor is Glioblastoma Multiforme (GBM), which exists in two forms: primary and secondary. Primary GBM arises from normal glial cells, while secondary GBM develops from anaplastic astrocytoma [11 - 14]. Despite the advent of advanced targeted therapies and immunotherapies, the five-year survival rate for GBM remains low, estimated between 4% and 7% [15 - 18]. GBM is typically diagnosed in patients in their mid-60s, with a higher incidence in men—approximately 1.6 times that of women. Studies report an occurrence rate of 1.1 to 5.0 cases per 100,000 individuals annually, with Caucasian populations exhibiting higher rates than Asian and African populations [17 - 22]. Recent data indicate a consistent and statistically significant increase in GBM across all age groups [19]. Early clinical signs of GBM are often non-specific and may include headaches, nausea, perso-

CHAPTER 5

Recent Advances in Systemic Chemotherapy for Malignant Brain Tumors

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Abstract: Recent years have seen tremendous advancements in the treatment of malignant brain tumors with systemic chemotherapy, providing fresh hope for better patient outcomes. The innovative chemotherapeutic drugs, targeted treatments, and combination regimens that have shown improved effectiveness and safety profiles are the main topics of this chapter's exploration of these state-of-the-art developments. The advent of blood-brain barrier-penetrant medications, customized treatment techniques based on genetic and molecular tumor characterization, and novel delivery systems including nanocarriers and convection-enhanced delivery are notable advances. Moreover, combining immunotherapy with conventional chemotherapy is emphasized as a possible way to beat tumor resistance and enhance treatment results. The chapter also explores ways to improve medication penetration *via* the blood-brain barrier and the processes underlying drug resistance. This chapter provides a thorough understanding of how these developments are changing the therapy landscape for malignant brain tumors through an extensive discussion of current clinical trials and forthcoming research. The chapter offers insights into prospective new paradigms in brain tumor care as well as future research initiatives by analyzing the incorporation of these innovative medicines into clinical practice. This summary of the most recent developments highlights how systemic chemotherapy may have a significant effect on the prognosis and quality of life of patients with malignant brain tumors, opening the door to more efficient and customized treatment approaches.

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Keywords: Blood-brain barrier, Malignant brain tumors, Nanocarriers, Personalized medicine, Systemic chemotherapy, Targeted therapy.

INTRODUCTION

Malignant brain tumors are a complicated and diverse group of neoplasms that grow inside the central nervous system (CNS). These tumors are notoriously difficult to treat because of their invasiveness, rapid growth, and propensity to infect adjacent brain tissue. The most common types of malignant brain tumors include medulloblastomas, gliomas (including glioblastoma multiforme), and lymphomas of the central nervous system. Gliomas, particularly glioblastoma multiforme (GBM), are the most prevalent forms of brain tumors in adults. GBM is particularly well-known for its high invasiveness and poor prognosis. On the other hand, medulloblastomas are associated with a higher incidence rate in children and are known to spread throughout the CSF [1].

The brain's supporting cells, or glial cells, are the source of gliomas. Based on histological characteristics and severity, they are divided into several categories; the most malignant type, grade IV astrocytoma, is assigned to glioblastoma multiforme. GBM still has a poor prognosis; after intensive therapy, average survival rates are just 12–15 months [2]. With advances in multimodal therapeutic techniques, kids who have medulloblastomas, which are the most prevalent aggressive brain tumor, have a better prognosis than GBM [3]. Medulloblastomas originate in the cerebellum.

Brain tumors that are cancerous and predominantly afflict those with compromised immune systems, including those living with HIV/AIDS or receiving organ transplants, are known as primary CNS lymphomas, or PCNSLs. With the introduction of high-dose methotrexate-based chemotherapy treatments, survival rates and overall prognosis in PCNSL have improved [4]. Single lesions are the typical presentation of PCNSL, although multiple tumors can also occur.

Historical Perspective on Chemotherapy for Brain Tumors

The development of chemotherapy for brain malignancies has been characterized by both major obstacles and slow progress. When brain tumors first appeared, the primary method of therapy was surgery, and patients with recurring or incurable tumors had few alternatives. One major hurdle to delivering successful chemotherapeutic drugs to the brain has been the blood-brain barrier (BBB), a selective permeability barrier.

The development of nitrosoureas, such as lomustine and carmustine, marked one of the first fundamental advances in brain tumor treatment in the 1970s and

1980s. These drugs showed promise in bridging the blood-brain barrier and offered patients with high-grade gliomas a moderate increase in survival [5]. Nevertheless, prolonged usage of nitrosoureas was restricted due to their related toxicity, which included lung fibrosis and bone marrow suppression.

Tezozolomide, an oral alkylating medication, was developed in the 1990s and completely changed the way malignant gliomas are treated. With its comparatively favorable adverse reaction profiles and capacity to pass the blood-brain barrier, temozolomide has become an essential tool in the treatment of glioblastoma. The 2005 landmark trial by Stupp *et al.* established the Stupp protocol as the gold standard of care by showing that the inclusion of temozolomide to radiation therapy substantially improved survival rates in patients with newly identified GBM [6].

Targeted medicines and immunotherapies have been more frequently used in recent years to treat brain cancers. Since bevacizumab can improve progression-free survival, the FDA quickly authorized it in 2009 for recurrent GBM. Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor (VEGF). However, this therapy did not considerably lengthen the median survival time [7]. Current research focuses on investigating immune checkpoint blockers and chimeric antigen receptor (CAR) T-cell therapies as means of using the body's immune system to combat malignant brain tumors [8].

Challenges in Treating Brain Tumors

There are still several obstacles in the way of treating malignant brain tumors. The blood-brain barrier (BBB), which limits the penetration of several systemic chemotherapeutic drugs into the brain parenchyma, is one of the main barriers. The brain needs the BBB's selective permeation to protect itself from toxins, but it also reduces the effectiveness of many possibly advantageous medications [9]. Another major obstacle is tumor heterogeneity. There is a great deal of epigenetic, genetic, and phenotypic variation in malignant brain tumors, especially glioblastomas, between people and even within a single tumor. The creation of efficient, broadly applicable medicines is made more difficult by this heterogeneity, which frequently results in resistance to therapy [10]. Furthermore, the hypoxic areas and the impact of adjacent glial and immunological cells in the milieu of brain tumors might alter the response to therapy while contributing to resistance mechanisms.

The precise position of brain tumors presents additional challenges. Because the tumor is close to brain regions that are important for language, movement, and thought processes, surgical resection—which is frequently a crucial part of treatment—may not be possible. Due to this restriction, it is necessary to strike a

CHAPTER 6

Dendrimer Technology: Current Advancements and Future Opportunities in Brain Tumour Detection and Management

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Abstract: A brain tumour is an uncontrolled cell proliferation, forming a mass of tissue composed of cells that grow and divide abnormally, seemingly beyond the control of the body's normal regulatory processes. Approximately 70% of primary malignant brain tumors diagnosed each year originate from glial cells. The physiological blood-brain barrier (BBB) impairs drug distribution to the tumour microenvironment and complicates the treatment of malignant brain tumours. Most of the conventional chemotherapeutics lack specificity and lead to serious systemic toxicity. However, nanocarriers have shown efficient therapeutic efficacy in delivering medications to the brain tumour cells. The targeting of nanocarriers to the tumour sites can be achieved by active or passive targeting. The dimensions and the physicochemical properties of the nanocarriers significantly affect brain permeability. Among various nanotools, branched PAMAM, PPL, and PPI dendrimers possess great efficacy in transporting chemotherapeutic agents across the BBB for treating brain tumours. This chapter discusses the various generations of dendrimers, their synthesis techniques, and the passive and active targeting strategies used to deliver chemotherapeutics to the tumour sites. The chapter also includes dendrimers as diagnostics and contrast agents in brain tumour diagnosis. Dendrimers have been established as remarkable in diagnosing and treating brain tumours, as they can transport the therapeutically active agents across the BBB to the cancer cells after systemic administration. Different dendrimers like PAMAM, PLL, PPI, carbosilanes, and phosphorus-based are used to develop novel therapeutics having prolonged and controlled drug release, immunotherapy, and anticancer activity. This chapter can provide remarkable guidance to scientists working on brain-targeting delivery systems.

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Keywords: Brain tumour, Dendrimers, Imaging, Passive and active targeting, Therapeutics.

INTRODUCTION

Dendrimers are branched macromolecules with bulky end-functional groups and a compressed molecular assembly. Each dendrimer has a central core molecule from which numerous branches extend, forming a well-defined and hierarchical architecture. The branches comprise recurring units or monomers chemically connected in a controlled fashion [1].

The chemical configuration and generation number of core, branches, and functional groups on the surface determine the dendrimer's shape, size, and reactivity. The word dendrimer was derived from a Greek term called “dendron”, which means “branching of a tree”. Dendrimers are branched, spherical, and symmetrical structures with defined shape and specificity, varying sizes from 1 to 15 nm. Dendrimers are primarily used to enhance the specific properties of a compound [2, 3] (Fig. **1**).

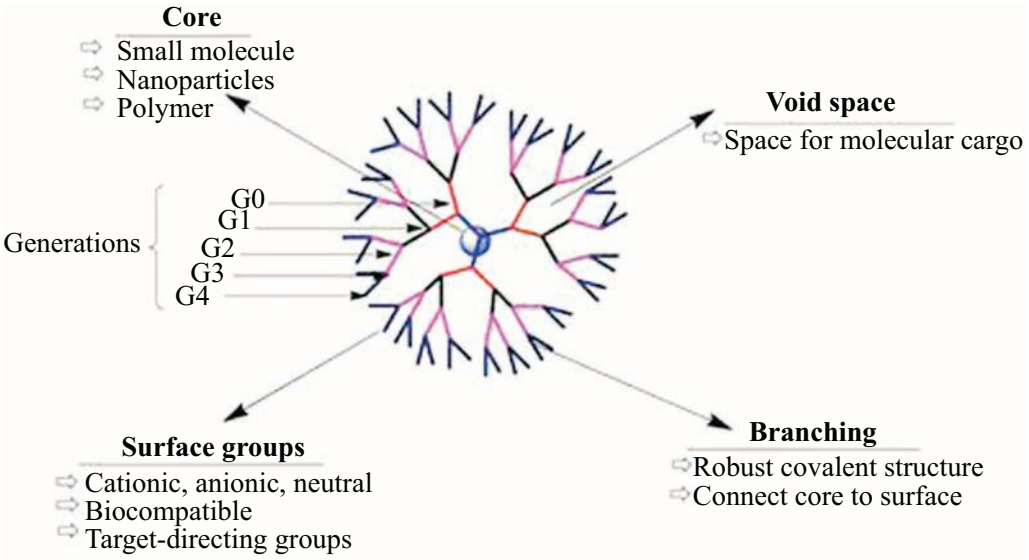

Fig. (1). Structure of Dendrimer (The dendrimer consists of three components: a core, interior layers with branching, and exterior surface functional groups).

Dendrimers are a fascinating class of molecules with unique properties that make them highly versatile for various applications. The key properties of dendrimers are as follows [2, 4]:

- **Well-defined Structure:** The dendrimer molecules of a particular generation are nearly identical in size and shape. This precise control over their architecture enables the tailoring of their properties with precision. Dendrimers can be synthesized as monodispersed materials.
- **Size and Generation:** The size of dendrimers is precisely controlled by the number of branching units, referred to as generation. Each generation features a doubling of the surface area and functionality compared to the previous one.
- **Functionality:** The outermost layer of a dendrimer, known as the periphery or surface groups, can be chemically modified with various functional groups. This allows researchers to design dendrimers for specific purposes, such as attaching drugs for targeted drug delivery or incorporating reactive groups for catalysis.
- **Host-Guest Inclusion:** The dense, branched structure of dendrimers creates cavities within their interior. These cavities can be hosts for encapsulating guest molecules, including drugs, imaging agents, or catalysts.
- **Biocompatibility:** Some dendrimers exhibit low cytotoxicity (minimal toxicity to living cells), making them potentially suitable for biomedical applications.

Dendrimers, due to their unique properties, are utilized in various fields. Their well-defined structure allows precise control, and their size can be tailored in generations. The external surface can be customized with specific functionalities for desired tasks, like attaching drugs. They can be tuned for water or oil solubility and hold guest molecules inside. Some are biocompatible, making them promising for medical applications.

Despite their advantages, dendrimers have some drawbacks. Certain types, particularly those of higher generation and cationic dendrimers, can be toxic to cells. Their complex structure makes them expensive to synthesize, and their behaviour in biological systems is still under investigation. This necessitates further research to optimize their biocompatibility and ensure safe use in various applications [5].

Dendrimers excel in nanotechnology due to their precisely tunable structure. Their hollow core and modifiable surface enable them to function as tiny delivery vehicles. They can carry drugs inside, protecting them until they reach their target. Surface groups can be designed to target specific cells, improving drug delivery and reducing side effects. This makes them promising for medicine, but they also have potential in sensors and catalysts. They are also being explored for gene therapy and diagnostics (Table **1**). However, research is ongoing to optimize their biocompatibility [6].

CHAPTER 7

Exploring the Role of Nutraceuticals in Brain Cancer Prevention and Treatment

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Abstract: Brain cancer remains one of the most challenging malignancies to treat, with limited therapeutic options and poor prognosis. Brain cancer, particularly gliomas, presents significant challenges due to its aggressive nature and limited treatment options. In recent years, nutraceuticals—bioactive compounds derived from food sources—have gained attention for their potential in preventing and treating various forms of cancer, including brain tumours. The growing importance of nutraceuticals in the treatment and prevention of brain cancer is examined in this chapter. Important components of nutraceuticals, like vitamins, carotenoids, polyphenols, and omega-3 fatty acids, show promise in the fight against cancer by regulating cell signalling pathways involved in tumour growth and metastasis, acting as antioxidants, and exhibiting anti-inflammatory effects. The chapter further delves into the dietary sources rich in these nutraceuticals, such as curcumin, green tea, ashwagandha, mushrooms, berberin, gasotile, and silibinin. By understanding the molecular mechanisms through which these compounds act, we can better harness their potential in integrative strategies for brain cancer management, ultimately improving patient outcomes. Understanding the molecular mechanism of action of any compounds at the cellular level is very important, as signalling proteins or proteins involved in the cell cycle can serve as therapeutic targets and also be used as biomarkers. Cell signalling proteins, such as ERK, JNK, p53, AKT, NF-kappa B, and cellular proteins CDKs, DAPK, and caspases, along with their roles, are discussed in this chapter. It also highlights the molecular changes caused by the nutraceuticals in brain cancer cell lines.

Keywords: Berberine, Brain cancer, Curcumin, Chemotherapy, Cell signalling, Epicatechin, ERK, Gastrodin, Nutraceuticals, p53, Silibinin, JNK.

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INTRODUCTION

Brain cancer, or primary brain tumors, refers to abnormal growths of cells within the brain or its surrounding structures. These tumors can be classified into primary brain tumors, which originate in the brain, and secondary (or metastatic) brain tumors, which spread from other parts of the body. Brain tumours vary widely in terms of their cell type, location, and growth rate. They are categorized into different grades based on their aggressiveness, ranging from benign (low-grade) to malignant (high-grade). Common types of primary brain tumours include gliomas (such as glioblastomas), meningiomas, and medulloblastomas. Secondary brain tumours often originate from cancers of the lung, breast, or melanoma. Brain cancer is challenging to treat due to its complex location and the sensitive nature of the surrounding brain tissue. The incidence of brain cancer worldwide is 3.0 per 100,000 for women and 3.9 per 100,000 for men, according to 2020 reports from the International Agency for Research on Cancer (IARC) [1]. Over 97% of glioblastoma patients pass away within five years after being diagnosed, according to reports [2]. Bioactive substances obtained from dietary sources are called nutraceuticals, and they offer additional health benefits. By combining the words “nutrition” and “pharmaceutical,” the term highlights their possible medicinal applications. For example, curcumin, resveratrol, green tea extract, and ashwagandha. It has been found that nutraceutical compounds can helpprevent chronic diseases and disorders, such as cardiovascular disease, diabetes, and cancer. Flavonoids, such as luteolin [3], fisetin [4], acetylapoaranotin [5], and astaxanthin [3], as well as lycopene from various sources including tomatoes, watermelons, grapes, and papaya [6], and GABA [7] are some examples of secondary metabolites exhibiting potential anticancer properties.

Bioactive components obtained from natural sources, known as anticancer nutraceuticals, have been shown to influence a number of biological processes that contribute to the development and growth of tumors, thereby potentially preventing cancer. These nutraceuticals can be found in foods, dietary supplements, and herbal preparations. Additionally, dietary antioxidants are known to be significant preventive factors against a number of cancers, such as liver cancer [8], colorectal cancer [9], and breast cancer [10]. However, the effect of dietary antioxidant vitamins against brain malignancies, especially gliomas, has received less academic attention [11].

Both the prevention and treatment of brain cancer can benefit significantly from the use of nutraceuticals. Recently, increasing attention has been directed toward nutraceuticals, natural substances extracted from plants, fruits, or cereals. These compounds are well-known for their antibacterial, anti-inflammatory, antioxidant, and antitumor properties [12]. Certain nutraceuticals may help lower the

probability of brain tumors by preventing the early stages of the disease's development. This is known as their potential chemopreventive qualities. Alongside standard treatments like chemotherapy, radiation, and surgical procedures, nutraceuticals may enhance therapeutic efficacy, minimize side effects, and improve overall quality of life. Moreover, chemotherapy and nutraceuticals together enable lower dosages of synthetic medications, reducing their severe adverse effects [12].

Certain nutraceuticals may specifically target cancer cells or molecular pathways involved in brain tumour growth and progression, offering a complementary approach to traditional treatments. A variety of nutraceuticals have recently been considered due to their unique ability to prevent tumor growth, including gliomas, by blocking the angiogenic process, cancer metastases, and apoptosis. By altering various pathways, nutraceuticals can cause cancer cells to malfunction. In reality, these substances have the ability to slow the development of cancer cells, prevent their angiogenesis and proliferation, and cause them to undergo apoptosis. They are also crucial at different phases of the therapeutic process. Regulation of cellular signaling pathways, including PI3K/Akt/mTORC1, JAK/STAT, and GSK-3, as well as other mechanisms, such as cytokine receptors, inflammatory pathways, reactive oxygen species, and miRNAs, may be one of the main objectives of nutraceuticals [13].

A list of nutraceuticals obtained from various sources that possess anticancer properties is mentioned in Fig. (**1**).

A potential alternative strategy for preventing brain tumours is offered using nutraceuticals.

By harnessing the therapeutic potential of bioactive compounds found in foods and supplements, they may provide supportive benefits to conventional therapies, improve patient outcomes, and contribute to overall cancer management strategies.

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Prashant Tiwari

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Sunil Kumar Kadiri

Dr. Sunil Kumar Kadiri is an experienced pharmaceutical sciences academician and researcher, currently serving as an Associate Professor at Dayananda Sagar University, Bengaluru. With over 18 years in academia, including five years as an Assistant Professor and 12 years as an Associate Professor, he has worked in prominent institutions in Hyderabad and Bengaluru. Dr. Kadiri earned his Ph.D. from JNTU Hyderabad in 2019, holds an M.Pharm in Pharmacology with distinction, and a B.Pharm from RGUHS, Bangalore. His expertise spans teaching, pharmaceutical research, and both pre-clinical and clinical studies. He has published over 80 peer-reviewed articles, many indexed in Scopus and Web of Science, focusing on drug-drug interactions, neuropharmacology, phytopharmacology, and herbal formulations. Additionally, he has authored numerous book chapters and textbooks and holds patents in India and the UK. Active in academia, he regularly participates in seminars and webinars, emphasizing psychopharmacology and public health, contributing significantly to drug development and therapeutic research.