Natural Products as an Alternative Therapy for Brain Tumors

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From Bench To Bedside

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Abstract

Incremental elevation in the trends of a brain tumor in recent years accounts for 5% adult population, whereas the number exceeds 70% in the case of children. Evidence reveals an eventual metastasize of 20%–30% of malignant tumors to the brain's different regions. Compression in the brain tissue and elevated intracranial pressure mediated by benign and malignant tumors contributed to severe consequences like the central nervous system (CNS) damage or even imperil the patient's life. Despite multiple therapeutic strategies in the market, none of the drugs are fully effective and safe. Strategic advancement indicates chemotherapy as a treatment of choice for critical conditions like brain tumors, but the chemotherapy drugs toxicity is still a major therapeutic hurdle. Plants and their derived natural products are one of the most emerging targets to strike against brain tumors. Analogs of several natural products are already demonstrated as antitumor in nature, and day by day, advancements unfold various other plant and plant derivatives having such antitumor activity. This chapter aims to underline and emphasize the antitumor agents, which can target brain tumors procured from the natural origin such as natural products and their analogs. The available data on different plants and isolated compounds of natural origin used to reduce and arrest brain tumors is also discussed here.

Keywords

Brain tumor · Anticancer agents · Alkaloids · Flavonoids · Cancer stem cells · Risk factors · Natural products

Introduction

A brain tumor is the atypical progression of the brain cells. The identification of "brain tumor" is based on the brain tissue such as "intracranial neoplasms, meningiomas, and lymphomas." Most of the intracranial tumors are similar in diagnostic, treatment approaches, and clinical presentations (Arvold et al. 2016). In this chapter, we will review the general appearance, diagnosis, and specific therapeutics for the brain tumor.

Clinical Presentation

Depending on the location and speed of growth of cells, tumors in the brain can represent generalized or focal neurological signs and symptoms such as hemiparesis, aphasia, headache, nausea, vomiting, and sixth-nerve palsy, respectively. The progression and period of symptoms also alter with the category of a tumor. This can also be diagnosed by using brain imaging. Tumors of the frontal lobe are characterized by dysphasia; tumors of the parietal lobe might manifest with numbness, spatial disorientation; and tumors of the optical lobe can cause visual defects. Tumors of infratentorial can represent the amalgam of cranial-nerve palsies, cerebellar disability, and long-tract signs (Ozawa et al. 2018). More than half of the patients reported headaches along with brain tumors. Mostly, the headache is not severe, but it can precisely locate the hemisphere in which the tumor is present. Normally, the headache starts in the morning and ends within a few hours even without treatment. It can be unilateral and can simulate migraines or even cluster headaches (Sperduto et al. 2012).

Brain tumors can also show some generalized signs and symptoms with the nonspecific anatomic location. It is reported that 50–80% of patients show seizures. It starts from local seizures but may lead to generalized and cause loss of consciousness. Studies showed that 30% of patients show headaches, and 15% of patients report increased intracranial pressure, severe headaches, specifically at night, whereas nausea and vomiting in the morning, blurred vision from papilledema, drowsiness, and horizontal double vision from the sixth cranial nerve palsies are also reported (Giulioni et al. 2014).

Diagnosis

Cranial magnetic resonance imaging (MRI) is the widely used method to examine a brain tumor. Moreover, other approaches particularly computed tomography (CT) cannot able to detect structural injury, especially in the posterior fossa, or low-grade gliomas. Therefore, MRI with gadolinium intensification is the test of choice.

Classification

World Health Organization (WHO) CNS tumor grading system classified the brain tumors from I to IV based on the histological criteria. They revised the classification in 2016 and put together significant genetic alterations of the molecular basis to the classic histology. This new classification or division gave rise to a new integrated diagnosis, in which histopathological name was accompanied by the genetic factors (e.g., glioblastoma, IDH-wildtype; panel) (Louis et al. 2016) (Table 1).

In case of conflicting results, the genotype presented more information compared to the histological phenotype. The application of molecular patterns enhances the diagnostic objectivity, accuracy, and results in more specific treatment.

Table 1 A basic WHO 2016 classification of specified tumors of neuroepithelial tissue origin

Sr. No.	WHO I	WHO II	WHO III	WHO IV
1. Astrocytic tumors (circumscribed gliomas)	• Pilocytic astrocytoma	• Pleomorphic xanthoastrocytoma	• Anaplastic pleomorphic xanthoastrocytoma	–
2. Diffused astrocytic and oligodendroglial tumors (diffuse gliomas)	–	• Diffuse astrocytoma, IDH-mutant • Diffuse astrocytoma, IDH-wildtype • Diffuse astrocytoma, NOS • Oligodendroglioma, IDH-mutant and 1p/19q-coDel • Oligodendroglioma, NOS	• Anaplastic astrocytoma, IDH-mutant • Anaplastic astrocytoma, IDH-wildtype • Anaplastic astrocytoma, NOS • Anaplastic oligodendroglioma, IDH-mutant and 1p/19q codeleted • Anaplastic oligodendroglioma, NOS	• Glioblastoma, IDH-wildtype • Glioblastoma, IDH-mutant • Glioblastoma, NOS • Diffuse midline glioma, H3 K27M-mutant
3. Ependymal tumors	• Subependymoma • Myxopapillary ependymoma	• Ependymoma	• Ependymoma, RELA fusion-positive • Anaplastic ependymoma	–
4. Neuronal and mixed neuronal-glial tumors	• Dysembryoplastic neuroepithelial tumor • Ganglioglioma • Gangliocytoma • Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos)	–	• Anaplastic ganglioglioma	–

Epidemiology

In 2017, the epidemiological factors of brain tumors were explained by the Central Brain Tumor Registry of the United States of America. They reported that about 2% of all cancers are primary brain tumors, with an annual prevalence of 22 per 100,000 population. The rate of incidence is more in people older than 85 years. In non-malignant brain tumors, meningiomas are the most reported type of brain tumor followed by tumors of the pituitary and nerve sheath. Gliomas account for 75% of brain tumors of malignant type, out of these, more than half are reported to be glioblastomas (Ostrom et al. 2017).

The number of cases of primary brain tumors also depends on ethnic origin, age, and sex. The incidence of brain tumors of malignant type, in particular, tumors of germ cell, gliomas, lymphomas, embryonal is more in men, whereas meningiomas and pituitary tumors occur more in women. In case of origin, for both sexes, the prevalence of primary brain tumors is higher in whites than in African individuals, except for meningiomas, pituitary tumors, and craniopharyngiomas. In the USA, the death rate of malignant primary brain tumors is 4.32 per 100,000 population with more than 14,500 deaths annually (Ostrom et al. 2017).

Risk Factors

Studies demonstrate that not more than 5% of cases of primary brain tumors owe to genetic syndromes, and they do not encounter recognizable risk factors. Literature reports that radiation ionization is the only other possible risk factor for primary brain tumors (Braganza et al. 2012). No additional environmental vulnerability or behavior has been observed. Some studies say that the use of cell phones also exposes a major risk for the beginning of brain tumors. Regardless of numerous large studies, no ultimate etiology for radiofrequency electromagnetic fields (RF-EMF), as well as the use of cell phones, has been confirmed for brain tumors. Multiple aspects trigger the pathophysiology of brain cancer. Simultaneously, various signaling pathways are altered during the induction, proliferation, and advancement of brain cancer (Kheifets et al. 2010) as depicted in Fig. 1.

Treatment

Surgical Management

For most primary brain tumors, safe surgical resection is the primary therapy with the goals of obtaining maximum accuracy, raising the quality of life and survival. Literature showed that the maximal safe surgical resection ameliorates operational level and decreases death rate in both high- and low-grade gliomas. The size of resection depends on several factors such as tumor spot, neurosurgeon skills, experience, and handling of pre- and intraoperative skills. For extensive safe

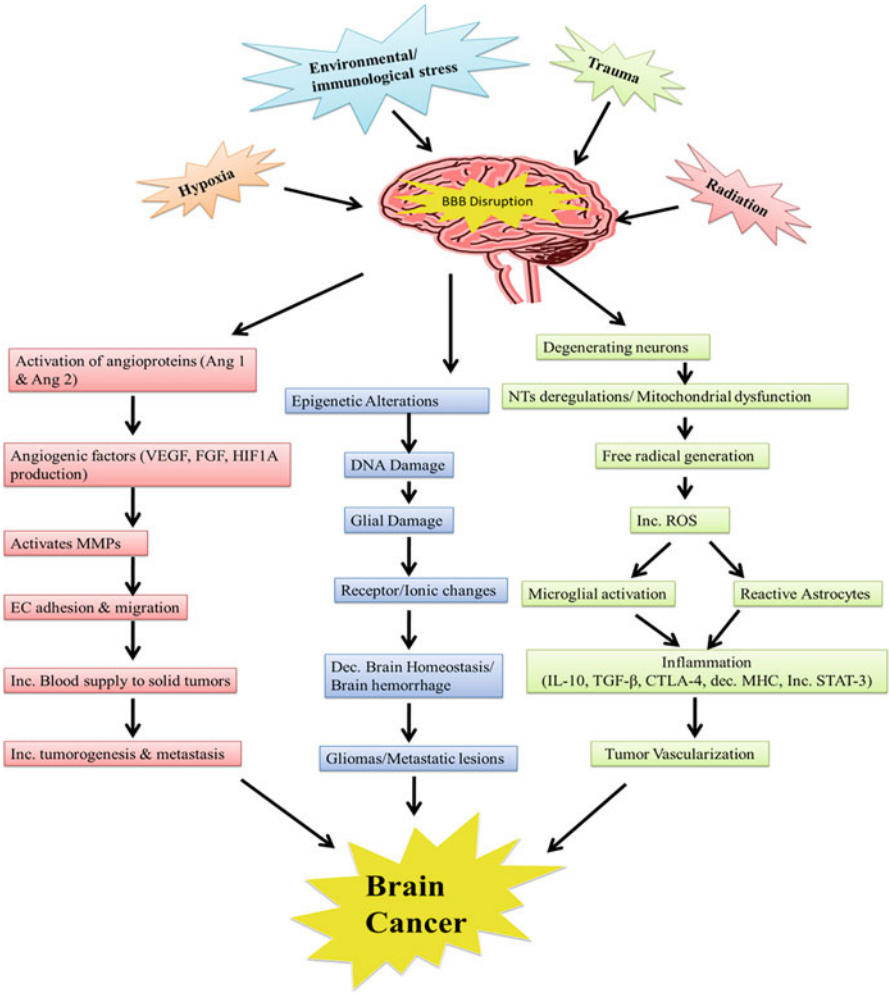

Fig. 1 Pathophysiology of brain cancer

resection, preoperative imaging techniques are always preferred, while awake surgery with intraoperative cortical electrode plotting remains the gold standard (van den Bent et al. 2017).

Upfront Management by Tumor Type

Pilocytic Astrocytoma (WHO I)

Pilocytic tumor of astrocytes is the most familiar and typical non-pervading low-category gliomas. It is mainly found in the optic pathway, spinal cord, and

cerebellum, the former being remarkably persistent among type 1 patients of neurofibromatosis. Total surgical resection is the principle treatment with the most favorable prognosis, and reported net survival as high as 100%, in comparison with 74% partially resected individuals (Bornhorst et al, 2016).

Diffuse Low-Grade Gliomas (WHO II)

Diffuse low-grade gliomas are comprised of diffuse oligodendrogliomas and astrocytomas. Maximal and early safe surgical resection is the primary therapy. Postoperative therapy findings are planted on the level of risk, although literature showed variable descriptions between low- and high-risk low-stage glioma (Jakola et al. 2017).

Patients at less risk of low-stage glioma are commonly younger than 40 years with no neurological conditions. A policy of watch-and-wait with MRI is approved for these patients every 3–6 months. A long-term analysis revealed the same rate of living with instant radiotherapy in contrast to advanced delayed radiotherapy (Weller et al. 2017).

Patients at big risk of low-stage glioma are usually more than the age of 40 years with neurological conditions. The standard of care after surgery is focal radiotherapy to 50-54Gy (Shaw et al. 2002) succeeded by six cycles of additional lomustine, vincristine, and procarbazine based on actively reported long-duration data of the phase III trial RTOG9802. This trial proved an increase in advancement-free living and net survival after treating with combination therapy. Median advancement-free living was raised from 4 to 10 years and median net survival progressed from 7.8 to 13.3 years (Buckner 2008).

Diffuse High-Grade Gliomas (WHO III)

Diffuse high-stage gliomas comprise anaplastic oligodendrogliomas and astrocytomas. Maximal safe resection is the proper care for high-stage glioma patients followed by chemoradiation. Chemoradiation comprises the radiotherapy to 60 Gy with either six cycles of additional lomustine, vincristine, and procarbazine or temozolomide (van den Bent et al. 2017).

Glioblastoma (WHO IV)

The most toxic form of a primary brain tumor in adults is glioblastoma. It was reported that the survival rate is about 5 years in only 5% of patients. Three clinical trials in phase two have reported an improvement with radiotherapy alone. The patients having a good performance status (Karnofsky performance status [KPS] $\geq$60), radiotherapy to 60 Gy over 6 weeks with temozolomide daily, succeeded by at least six cycles of additional temozolomide (5 days over 21 days cycle) has been the

principal standard of care. The patients aged more than 70 years with glioblastoma are considered not to be applicable to take the typical 6-week radiotherapy course. Hypofractionated or a higher dose of radiation therapy with additional temozolomide was currently reported to be predominant to alone hypofractionated radiation therapy and lessen the treatment duration without compromising the quality of life (Perry et al. 2017).

Natural Products as Anticancer Agents

Cancer is a frightful disease leading to remarkable destruction in the living population. Cancer chemoprevention and treatment are the earliest need for today's population to deal with such worldwide attention. Natural products are overcoming the research for such diseased conditions. The treatment with natural products and their metabolites has flagged away towards the new hope of treating such disorders. Natural products and their metabolites are the emerging strategies to prevent, delay or cure a wide range of cancers. Here, we will discuss the different plant or natural products and their metabolites with their possible mechanisms for the management and cure of a group of cancers. Natural products such as phytochemicals (bittersweet, andrographolide, plumbagin, etc.) and their secondary metabolites (include alkaloids, flavonoids, saponins, resins, latex, etc.) are the recent approaches in view of treating cancers (Cragg and Pezzuto 2016). Several researchers are in line to find health-promoting phytochemicals from different products such as vegetables, fruits, herbs, nuts, tea, stems, flowers, seeds, and spices. Traditionally more than 80% of the population use plant-derived natural compounds with a rich source of anticancer natural compounds. The literature demonstrates that more than 50% of clinically used drugs are either natural products or their derivatives which consist of plant-derived active ingredients. These compounds work by regulating the pathways of cell death in particular autophagic, intrinsic, and extrinsic pathways such as isoflavones and phytoestrogens deactivate the NF-κB, apoptosis induction, and angiogenesis inhibition (Upadhyay and Dixit 2015).

Alkaloids as Anticancer Agents

Cancer refers to the world's second most fatal disease defined by groups of diseases. The cell's irregular growth and division give rise to cancerous cells. Instead of having a large number of therapeutic agent's existence, still there is an urge for the development of newer therapeutic agents with greater therapeutic efficacy and lesser toxicological profile. The recent research and available literature pave a new way toward the involvement of natural products in the treatment of a number of diseases. The food obtained from plants exhibits variation in their nutritional content profiles, as they are the good sources of key nutrients (i.e., vitamin C, carotenoids, minerals, folate, etc.) and to an extent well-marked bioactive composites (phytochemicals) (Issinger and Guerra 2021). The phytochemicals and other secondary metabolites

have been now reported to be the better source for the discovery of anticancer agents. Thus, plant products such as alkaloids represent a wider chemotherapeutics with a cyclic structure having a nitrogen atom in the search for anticancer agents (Shu et al. 2010). The nitrogen atom present in the ring structure imparts basicity to the chemical compound. In addition, other atoms may also show their presence in the chemical structure of the compound, thus, are classified based on chemical structures, biosynthetic pathways, etc., and are implicated to investigate these compounds. Alkaloids are the major constituents obtained from the higher plants and exhibit wider therapeutic actions, for instance, ephedrine obtained from ephedra to be used for the treatment of asthma. Morphine from opium poppy is employed as a single model of analgesic and anticancer actions of vinca alkaloids such as vinblastine and vincristine are well described. Camptothecin and vinblastine along with newly discovered alkaloids suggest that alkaloids are highly therapeutically active compounds having a natural origin. Therapeutically active alkaloidal constituents from different plants such as *Solanum schimperianum, Rauwolfia vomitoria, Tylophora indica, Enicosanthellumpulchrum, Ancistrocla dusheyneanus, Ambelania occidentalis, Menisperm undauricum, Macleay acordata, Peganum harmala, Oxytropis kansuensis, Catharanthus roseus, Berberis aquifolium, Piper longum, Piper nigrum, Morindap ubescen, Nothapody tesnimmoniana,* and *Toddalia asiatica* are yet to be demonstrated as anticancer agents (Choudhari et al. 2020).

- **Certain Alkaloids with Their Anticancer Mechanisms.**
- **Berberine.**

Berberine obtained from *Rhizoma coptidis* is a widely prescribed Chinese herb. Berberine is chemically isoquinoline, mostly derived from natural herbs. It possesses sustained therapeutic activities, in particular antibacterial, antidiabetics, sedative, anti-inflammatory, antiulcer, blood vessel dilation, blockade of platelet assembly, neuroprotective, and hepatoprotective effects. The utilization of berberine has been carried out in neurasthenia, diarrhea, diabetes, arrhythmia, and various other diseased conditions. Multiple evidence has shown that berberine acts by altering various pathological pathways involved in the development and progression of tumors in studies particularly in vivo and in vitro (D'Arcy 2020).

Berberine acts by seizing the movement of tumor cells from one part to another and by inhibiting tumor invasion. Targeting toward the signaling pathways, berberine also inhibits the initiation of the nuclear factor κ-light-chain enhancer of activated B cells (NF-κB) that also activates the other pathways, in particular, the generation of reactive oxygen species (ROS) and regulates pathways of oxidative stress in cancer cells (Ayati et al. 2017). The abovementioned pathways may target different types of tumors including a brain tumor.

- **Evodiamine.**

Evodiamine is chemically a quinolone alkaloid, obtained from the herb *Evodia rutaecarpa*. Evodiamine possesses a wide range of therapeutic benefits, in particular,

anti-anxiety, anti-allergic, antinociceptive, anticancer, and anti-inflammatory effects. It also possesses vasodilating properties and cardioprotective effects. Evodiamine induces cell cycle arrest or apoptosis, suppresses angiogenesis, the proliferation of tumor cells, and the movement of cells from one part to another one in a variety of cancer cell lines in vitro and in vivo experiments (Yang et al. 2017). Evodiamine activates caspase cascade and triggers apoptotic pathways, and thus, downregulates Bcl-2 and increases Bax expression in onco cells. The phosphatidylinositol 3-kinase/Akt/caspase and Fas ligand (Fas-L)/NF-κB mechanistic pathways may also trigger evodiamine-mediated cell death of the cancerous cells. In addition, the mechanistic approaches targeting the onco-cells may also be upregulated by the ubiquitin-proteasome pathway (Guo et al. 2019). Such mechanistic approaches suggest the various cancer-protective activities of evodiamine.

- **Piperine.**

Piperine is a secondary alkaloid and an active compound of various spices. It is chemically piperidine, isolated from *Piper nigrum* and *Piper longum* that have been used for decades. Piperine exhibits a wide variety of therapeutic activities discussed next. It exhibits antioxidant, hypolipidemic, anti-inflammatory, antidiarrheal, anti-convulsant, antimutagenic, central nervous system depressant properties, and tumor inhibitory activities. The chemopreventive properties of piperine against different types of carcinogens, such as benzo(a)pyrene and 7,12-dimethyl benz(a)anthracene, exhibit its potential as a cancer-protective agent. Piperine targets different signaling mechanisms such as NF-κB, c-Fos, cAMP response element-binding (CREB), activated transcription factor 2 (ATF-2), in different cancerous cells. It inhibits PMA-induced MMP-9 expression by inhibiting PKCα/extracellular signal-regulated kinase (ERK) 1/2 and decreasing NF-κB/AP-1 stimulation. Noteworthy, piperine also downregulates the functioning of different proteins that include P-glycoprotein (P-gp) and CYP3A4, affecting the metabolism and also re-activates multidrug-resistant (MDR) oncocells (Do et al. 2013). Piperine is thus involved in a number of useful therapeutic pathways that may suggest the role of piperine in anticancer activities.

- **Other Alkaloids.**

Besides the abovementioned alkaloids, other alkaloids such as chelerythrine isolated from *Toddalia asiatica* (L.) Lam, chelidonine extracted from *Chelidonium majus* L., fagaronine isolated from *Fagara zanthoxyloides* Lam., lycorine obtained from *Lycoris*, nitidine chloride from *Zanthoxylum nitidum* (Roxb.) DC., solanine obtained from *Solanum tuberosum*, sophocarpine extracted from *Sophora alopecuroides* L., and trigonelline isolated from *Trigonella foenum-graecum* may also exhibit anticancer properties with different mechanisms (Mondal et al. 2019). However, studies involving the direct effects of alkaloids as anticancer agents are limited, and thus, these need to be explored yet. The various alkaloids obtained from different plant sources are enlisted in Table 2.

Table 2 List of alkaloids derived from different plant sources

Sr. No.	Plant	Alkaloids
1.	*Rauwolfia vomitoria*	Serpentine, alstonine, reserpine
2.	*Piper longum*	Piperlongumine
3.	*Enicosanthellum pulchrum*	Anoniane, scoulerine, Liriodenine
4.	*Menispermun dauricum*	Dauricine, Daurisoline
5.	*Macleaya cordata*	Chelerythrine chloride
6.	*Oxytropis kansuensis*	Swanosine
7.	*Catharanthus roseus*	Vincristine, Vinblastine
8.	*Berberis aquifolium*	Berberine
9.	*Ancistrocladus heyneanus*	Ancistrocline
10.	*Solanum schimperianum*	Solanopubamine
11.	*Morinda pubescens*	Hyoscyamine
12.	*Nothapodytes nimmoniana*	Camptothecin
13.	*Peganum harmala*	Harmicine
14.	*Toddalia asiatica*	Noddalia asiatica
15.	*Piper nigrum*	Piperidine
16.	*Tylophora indica*	Tylophorine, Tylophorinine
17.	*Ambelania occidentalis*	Vincamine
18.	*Camptotheca acuminata*	Camptothecin
19.	*Curcuma longa*	Curcumin
20.	*Evodia rutaecarpa*	Evodiamine
21.	*Sophora flavescens*	Matrine
22.	*Sanguinaria canadensis*	Sanguinarine
23.	*Stephania tetrandra*	Tetrandrine

Flavonoids as Anticancer Agents

Flavonoids are plant-derived phenolic compounds widely distributed in 10 chemical groups (Yao et al. 2004). Among all of them, anthocyanins, flavanones, flavanols, isoflavones, and flavones are especially regular in the diet. Many flavonoids exhibit the property of suppression toward carcinogenesis in different animal models. The major groups of diet intake for flavonoids are flavonols (viz. quercetin, kaempferol), onion lavished, broccoli, flavones (viz. luteolin, apigenin), which are contained in celery and parsley, flavanones (e.g. naringenin, hesperetin), which are chiefly found in citrus fruits and tomatoes, isoflavones (viz. genistein, daidzein), which are chiefly found in soya-related products, flavanols (viz. catechin, epicatechin, epigallocatechin, epigallocatechin gallate (EGCG)), which are abundant in red wine, chocolate, green tea, and anthocyanidins (viz. cyanidin, pelargonidin, malvidin), obtained from berry fruits and red wine (Yan et al. 2021). Out of these, *Camellia sinensis* (tea), *Vaccinium* spp. (blueberry), *Theobroma cacao* (cocoa), and *Vitis vinifera* (grape) have shown their protective actions on mental performance and vascular activity. A number of flavonoids (e.g., quercetin, apigenin, tea catechins) possess anti-

inflammatory action by suppressing inducible nitric oxide synthase (iNOS) and cycloxygenase-2 (COX2) enzymes. Flavonoids have good anti-inflammatory and growth inhibitory activity as they target COX and iNOS, major therapeutic targets of inflammation in cancer cell lines. Flavonoids have also been shown to affect cell signaling and its progression in various in vitro cell line studies. For instance, tea flavonoids suppress epidermal growth factor (EGF) and platelet-derived growth factor-derived signal transduction pathways especially by striking the suppression of events in particular angiogenesis. Genistein and Quercetin suppress the protein tyrosine kinase (trk), which is also engaged in tumor cell progression. In addition, other flavonoids, luteolin, quercetin, and apigenin are known to give rise to cell cycle suppression and apoptotic cascade by a p53-associated mechanism. In concise, numerous mechanisms have been found for the anti-neoplastic action of flavonoids, in addition to anti-inflammatory, antioxidant, and antiproliferative properties, bioactivation enzymes suppression, and introduction of detoxifying enzymes (Prasad et al. 2010). However, such outcomes were often found with concentrations that are more than what can be achievable in humans via dietary means.

- **Major mechanisms of flavonoids targeting brain cancer**
- Inhibition of neuroinflammation
- Interaction with MAPK signaling cascade
- Interaction with PI3 Kinase signaling pathway
- Decreasing ROS and oxidative stress

Saponins as Anticancer Agents

Saponins are chemically derived glycosides with spirostane or triterpenoid aglycones that exhibit different therapeutic actions against human diseases. These triterpenoid saponins have a natural origin that exhibits anticancer properties (saikosaponins and ginsenosides) and steroid-derived saponins (polyphyllin, dioscin, and timosaponin) extracted from different Chinese drugs. Saponins also inhibit angiogenesis, metastasis, and proliferation of tumor cells. Saponin is also known to have anti-multidrug-resistant effects, induce autophagy, and also target various other signaling pathways. Many saponins are evaluated for their use in medicine such as *Olea europea* (Oleacea), leaves of *Viscum album* (Loranthaceae), buds of cloves (*Syzygium aromaticum*, Myrtaceae), Lucerne plants (alfalfa, *Medicago sativa*), and soya saponins. These plants are widely used for their anticancer properties (Fitrilia et al. 2015).

- **Panax notoginseng (LPNS).**

Ginseng, especially the root part of Panax ginseng, is a very well-known traditional herb possessing medicinal properties and widely utilized for the cure of multiple diseases by boosting vitality, nourishment to the bodily resistance to invaders, give rise to body liquids and decreases thirst, mitigates the mind and

body comfort, reducing body weight, benefiting intelligence, and prolonging life. Ginsenosides are the secondary metabolites and biologically active constituents in ginseng. Various evidence suggests that ginsenosides possess many neurotrophic and neuroprotective properties, enhance neural stem/progenitor cell (NSC) progression, and progress outgrowth of neurite and neuronal network formation. The in vitro studies suggest that ginsenosides exert protective effects through their antioxidant and neuroprotective actions. It has shown better therapeutic efficacy in various studies that includes TBI, recovery of neurological functions in particular learning and memory (Rastogi et al. 2015). Thus, the use of these ginsenosides could be fruitful in studying and managing various brain tumors.

Rosmarinic Acid

The saponins obtained from rosmarinic acid, a Fyn inhibitor explored in human-derived U251 and U343 glioma cell lines. Rosmarinic acid decreases the expression of certain factors such as matrix metalloproteinase, mainly MMP-2 and MMP-9, decreases proliferation rate, also inhibits the spread of the oncoproteins. Thus, it is a potential drug candidate to be involved in brain tumor studies (Liu et al. 2021).

Cannabis and Cannabinoids

Cannabis sativa L. is a well-known plant of the Cannabaceae family and also it is widely spread all over the globe. It is in use since prehistoric hours. Aside from this herb and its products, majorly three categories of cannabinoids (CBs) are known, namely, endocannabinoids, plant cannabinoids, and derived cannabinoids. Cannabinoids stand in the way of the endogenous cannabinoid system (ECS), the chief constituents of which are CB1 and CB2 receptors and the endocannabinoids 2-arachidonoyl-glycerol (2-AG) and anandamide (AEA) derived products. Nonetheless, from its recognition in the 1990s, many secondary targets and ligands have been observed. These comprise G-protein coupled receptor GPCR55, peroxisome proliferator-activated receptors (PPARs), transient receptor potential calcium channels (TRPs), and adenosine receptors, and enzymes for degeneration (e.g., fatty acid amide hydrolase [FAAH]) or synthesis (e.g., diacylglycerol lipase [DAGL]) (Martell et al. 2018). Cannabinoids reduce the pace of tumor advancement, migration, and spread by suppressing tumor angiogenesis. These are found to suppress MMPs and also by instigating caspase-mediated cell death of cancer cells. Cannabinoids alter the ECS via allosterically inhibiting CB1 receptors, cause induction of TRPV1, acts via 5-HT1A serotoninergic receptor by inhibiting GPCR55, and slowing down the breakdown of AEA by suppressing FAAH. CB also possesses anxiolytic, analgesic, and antidepressive actions similar to that of tetra-hydrocannabinoid (THC). In many cancer studies, the synergistic effects of different combinations of cannabinoids were more useful (Soderstrom et al. 2017). The difference in the antitumor activities of CB thus acts via different targets and may act as potential therapeutics to be used in various

malignancies. Cannabinoids may serve to increase the life expectancy of brain cancer patients by targeting the progression and distribution of cancer cells in their bodies.

Neurostatins in Brain Tumor

In brain extracts, neurostatin is a ganglioside that regulates astroblast and astrocytoma division. The modified gangliosides, for instance, O-acetylated, in the terminal sialic acid found in very minute quantities in the CNS, where they appear to express different signaling pathways during growth and in adulthood. Hence, they might be engaged in either stimulation or inhibition of tumor development. Suppressing the role of neurostatins on cell division and advancement is associated with the modulation of the reaction to various growth-promoting factors. The major outcome of EGFR stimulation in oncocells is the transfer of signals to enhance cell division and multiplication. This mechanism has profound consequences in halting cell division, advancement, and having pro-apoptotic, antiangiogenic, and antiinvasive properties (Valle-Argos et al. 2011). Thus, based on the above evidence we can conclude the beneficial role of neurostatins in the management and treatment of gliomas.

Latex and Resins in Brain Tumors

Latex and resins are important in controlling tumor growth. Resins release few secondary components which enter the brain and acts via different targets. Incensole acetate is one of the key resin components which stimulates transient receptor potential vanilloid channels in the brain and thus arrest the cell cycle and tumor progression (Vengoji et al. 2018).

Guduchi

Tinospora cordifolia, also known as Guduchi, is a member of the Menispermaceae family. For centuries, it has been used in Ayurvedic medicine to treat jaundice and preserve liver function. It also has antiangiogenic, anticancer, anti-inflammatory, and radiosensitizing properties. Ethanolic extract of Guduchi EEG prevents the development of C6 rat glioma cells and U87 GBM cells in a concentration-dependent manner, as well as triggered astrocyte-like differentiation of C6 cells. EEG also blocked C6 cell migration and invasion, which was linked to lower expression of matrix metalloproteinases-2 and -9 (MMP-2 and MMP-9), NCAM, and PSA-NCAM. Also, EEG-induced cell division and cell aging were associated with lower levels of cyclin D1, Bcl-xL, and higher levels of mortalin, a senescence detector (Sharma 2019). That's how Guduchi suggests its role in various malignancies.

- ***Boswellia* Gum Resins.**

In India, *Boswellia* species are widely distributed. Its genetic variation, segregation among and within-population are responsible for the differences among *Boswellia* species. The gum-resin is produced by a variety of species belonging to the genus *Boswellia*, a group of plants with resin-bearing ducts. The main active additives sabinene, cembrene, incensole, incensyl acetate, and verticillia, as well as amyrin and amyrenone are believed to have anticancer potential, and thus, maybe a novel treatment for brain tumor management (Efferth and Oesch 2020).

Bittersweet in Brain Tumors

Bittersweet, or *Celastrus orbiculatus*, is a member of the Celastraceae family is well known to manage and treat a variety of ailments, like joint disorders specifically rheumatoid arthritis. *Celastrus* and its components have been shown to have free radical scavenging, anti-inflammatory, and tumor-fighting properties. By upregulating the PI3K/Akt/mTOR signaling pathway, *Celastrus orbiculatus* extract (COE) was proven to suppress cell growth, adhesion, and malignancy in human gastric malignant cells, as well as trigger apoptotic cell death and autophagy in colorectal cancer cells. COE also reduced cell viability, adhesion, migration, and invasion in U87 and U251 GBM cells as per Hao et al. Although the role of the PI3K/Akt/mTOR signaling in managing migration and movement in both GBM cell in vitro models was not specifically investigated in this study, the participation of this mechanism in controlling invasion and motility in both GBM cell models suggests that COE may be impeding the PI3K cascade. More mechanisms and research is required to explore its role in cancer (Phillips et al. 2019).

Andrographolide and Brain Tumors

Andrographolide (Andro), a diterpenoid lactone obtained from the herbal treatment *Andrographis paniculata*. *Andrographis paniculata* (AP) is commonly known in India as Kalamegha or Kalmega. Andrographolide, a secondary metabolite derived from the leaves of AP, has been known to have anticancer properties against a variety of malignancies, as well as the ability to cross the BBB. It possesses anti-inflammatory and anticancer effects (Mussard et al. 2019). Andrographolide's potent inhibitory effect on the JAK-STAT3 mechanism could make it a promising anticancer agent. The inhibition of STAT3 activity by andrographolide improved tumor cell chemosensitivity to doxorubicin, indicating that andrographolide could be used in conjunction with traditional chemotherapeutics to kill cancer cells. Many researchers have been attracted to andrographolide and its derivatives because of their impressive anticancer property and cytotoxicity in vitro and in vivo, which suggest that they play a significant role in potential chemotherapeutic strategies. As a result, further

andrographolide toxicological studies are necessary before it can be tested in full-scale clinical trials (Islam et al. 2018). Andro could prove a beneficial cancer-protective agent shortly if it is validated in human clinical trials.

Plumbagin in Brain Tumors

Plumbagin is a bicyclic naphthoquinone found in plant roots belonging to the Droseraceae, Plumbaginaceae, and Ebenceae families. It is a member of a large and broad group of plant species. Antidiabetic, antioxidant, antimutagenic, anti-inflammatory, and antiproliferative effects of this natural compound are effective toward leukemia, melanoma, lung, breast, as well as prostate cancer. Plumbagin's inhibitory response is characterized by upregulating Akt/mTOR, NF-kB, and JNK signaling pathways (Yin et al. 2020). Its impact on GBM cells was extensively explored, discovered that plumbagin caused cell growth inhibition and DNA breakage, accompanied by cell death. Increased expression of TNFRSF1A, PTEN, and suppression of E2F1 genes, MDM2, cyclin B1, survivin, and Bcl2 protein expression, as well as enhanced caspase-3/7 activity, were discovered in the mechanistic studies As a result, it has been proposed that incorporating plumbagin with other anticancer drugs to create "hybrid drug molecules" may lead to the development of novel and effective anticancer drugs with positive action toward brain malignancies (Yin et al. 2020). The plant-derived chemical constituents and secondary metabolites showed different targets for cancer as discussed above. A few of them are depicted here in Fig. 2.

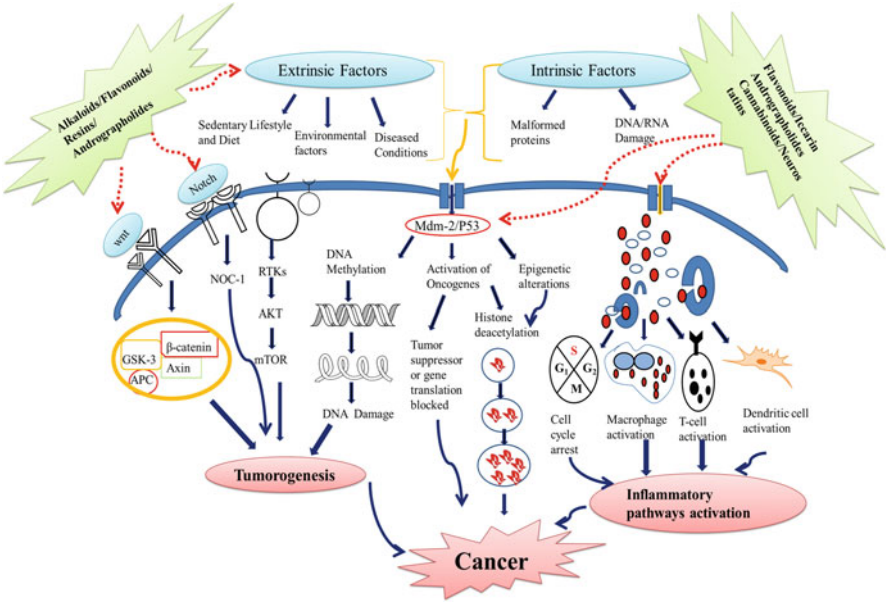

Fig. 2 Mechanisms of various phytochemicals targeting brain cancer

Natural Products and Blood–Brain Barrier

- **Flavonoids.**

Flavonoids are classified under a vast classification of secondary metabolites of plants. Flavonoids are obtained from metabolites and found in fruits, vegetables, tea, wine, and others and are also very well utilized for their antioxidant property, regulates the release of cytokines, acts against various microbes, and antitumor effects. Quercetin is also an important metabolite of the St. John's Wort (*Hypericum perforatum*) flowering plant, used as herbal medicine for mild depression. Quercitin exhibited an approach to reach the central nervous system depending on its penetration to the blood–brain barrier (BBB) that depends on different efflux proteins, like Bcrp as suggested in both in vitro and in vivo studies. From a recent in vitro study approach, it has been concluded by using primary rat brain endothelial cells and immortalized human brain endothelial cells (Wang et al. 2021) that a selective inhibitor of glycogen synthase kinase-3 increased beta-catenin and enhanced expression of P-glycoprotein including induction of the initiator of MDR1. This increases P-glycoprotein-regulated outflux ability, while down-regulation of this signaling using quercetin, reduced the expression of P-glycoprotein (P-gp). Moreover, some same results were obtained with Mrp 4 and Bcrp, which are situated at the blood–brain barrier (BBB). Thus, could target brain cancer. Although there are not any such serious side effects of quercetin which are evidenced in several studies and also it has been stated that after oral ingestion, its plasma concentrations cause dysregulation in efflux channels at the blood-brain barrier (Khadka et al. 2021).

The Naringenin is a very well-known flavanone, originated from the grapefruit and also binds with P-gp at the BBB (Joshi et al. 2018). Although in addition to cyclosporin A, it does not enhance the AUC of co-administered camptothecin in the brain. Naringenin and its metabolites affect the CYP450 and interfere with efflux mechanisms and thus affect ADME of a wide range of therapeutics in the gastrointestinal tract.

Glabridin is an isoflavone obtained from liquorice root. It targets various CVS and CNS diseases. Additionally, levels of glabridin in the brain increase when verapamil or quinidine is administered in combination. Moreover, in the brain, the concentration of glabridin in mdr1a(−/−) mice was six times higher when compared to wild-type mice, suggesting that P-gp restricts the diffusion of glabridin in the brain through the BBB and could lead to the potential target for resistance to glabridin (liquorice) treatment for neurovascular diseases (Rendic 2021).

- **Naphtodianthrones and Phloroglucinols.**

Naphtodianthrone and prenylated phloroglucinol are the major secondary metabolites of St. John's wort, scientifically known as *Hypericum perforatum*, useful in treating neuropathic pain, wound healing, and depression. Though, hypericin as an inhibitor for dopamine, α-hydroxylase, leads to the rise in the levels of dopamine

(Iqbal and Ansari 2019). Hyperforin has been known to exhibit the inhibition of 5-HT, dopamine, noradrenaline, GABA, and glutamate uptake.

- **Cytostatic Agents.**

The cytostatic agents are mainly used as therapeutic agents for cancer treatment due to their property to inhibit cell proliferation. They comprise many natural products or their derivatives involving intercalating anthracyclines, antibiotic agents, topoisomerase inhibitors, and others (Liang et al. 2019). It was observed in recent studies that repetitive treatment of doxorubicin increased the constitutive expression of P-gp, which results in the efflux of doxorubicin, not only in the brain cancer cells but also in the endothelin of vessels. Thus, binding by P-gp might show a powerful mechanism to enhance the levels of doxorubicin in brain cancers.

Vinca alkaloids, which are obtained from the *Catharanthus roseus*, or *Vinca rosea*, have a specific site to bind at specific proteins on tubulin and shows its activity by inhibiting the assembly of tubulin into microtubules. They are also very well-known substrates of ABC-transporters in the blood–brain barrier and act as a competitive agonist for binding and transport by the efflux proteins (Chaves et al. 2017).

Etoposide, a glycoside derivative of podophyllotoxin, was obtained from the roots of evergreen American mayapple (*Podophyllum peltatum*). It is a very well-known target of p-gp and also Mrp1, which shows its expression at epithelial cells (Amawi et al. 2019).

- **Tanshinones.**

Tanshinone II-A (TSA) and Cryptotanshinone are the two important lipid-miscible components of Danshen, the dried roots of *Salvia miltiorrhiza* Bunge, which is mainly used as a treatment therapy for cerebrovascular diseases involving stroke and less commonly Alzheimer's disease. Furthermore, in an in situ rat brain perfusion model, the brain perforation of TSA was also enhanced in the availability of Mrp1/2 or Pgp blockers (Poku 2021).

- **Boswellia.**

Boswellic acids are the major components of *Boswellia serrata* which are collecting greater attention for the treatment of inflammation and decrease in peri-tumoral edema, involving edema of the cerebral. According to a recent study, there is a report that keto derivatives such as 11-keto-beta-boswellic acid, boswellic acid, and acetyl-11-keto-beta-boswellic acid intact with P-gp. They are known to inhibit the transport process of P-gp in porcine brain capillary endothelial cells, but no modification was noticed using boswellic acids which contain no keto group (Efferth and Oesch 2020). The significant suppression of P-gp at the blood–brain has no relevance for other P-gp substrates present in the brain, due to the lower plasma levels of boswellic acids (Bordoloi et al. 2017).

- **Digoxin.**

Digoxin has been evidenced to be a very well-known P-gp and Oatp2 substrate; both are significantly present at the blood–brain barrier. A recent study demonstrated an explanation, which was suggested that quinidine also inhibited the mechanism, through which the digoxin uptakes into the brain, and it was observed in the lack of P-gp–driven efflux, and the communication with Oatp2 was shown as one the major probability (Veszelka et al. 2018).

Natural Products on Cancer Stem Cells

Among several tumors, glioblastoma (GBM) is one of the prevailing lethal tumors of the nervous system. The glioblastoma stem cells provide their contribution in the initiation of the tumor, the spread of tumor, reappearance, and in developing resistance in the treatment of cancer. GBM utilizes autophagic processes for the livelihood of cells when treated with cancer-causing agents, involving irradiation. Therefore, it is considered a novel efficacious therapy. The increasing data suggest that dysregulation of microRNAs (miRNAs) in cancer cells and cancer stem cells (CSCs) reflects different profiles of miRNA in several types of tumors, also in GBM. In recent studies, several in vivo and in vitro studies have provided insight into the target of isatin, a phyto-compound in neuroblastoma condition (Cong et al. 2019). There are varieties of natural products including resveratrol, gambogic acid, oxyresveratrol, aneglicin, and 18α-Glycyrrhetinic acid, which activates apoptotic processes and further initiates autophagy of the cancer cells in the brain.

- **Natural Products on Brain Cancer Stem Cells**.
- **Quercetin.**

Quercetin is a natural flavonoid known as an antioxidant and anticancer agent which is found in variety of vegetables such as broccoli, red onions, and fruits including apples, red grapes, cherries, and berries. Quercetin treatment significantly reduced the effectiveness of STAT3-mediated IL-6 in U87 and T98G cell lines in a graded response. It also improves the effectiveness of GBM cell lines U87 and U251 to TMZ by inhibiting the expression of heat shock protein 27 (Hsp27), which also leads to drug resistance. In addition, quercetin also shows programmed cell death in p53 mutant GBM cell line U373MG. In divergence to these anticancerous properties, a few cancerous effects of quercetin in a rat glioma animal model were also reported (Zamin et al. 2014).

- **Resveratrol.**

Resveratrol, which is known for its antioxidant property, is found in grapes, mulberries, and peanuts with well-evidenced antitumor activity. It expressively diminishes TMZ resistance via downregulating the expression of NF-κB signaling

in T98G GBM cells, also expresses the AMPK pathway, and inhibits the mTOR pathway. Resveratrol also markedly reduces the signaling of the antiapoptotic markers, X-linked inhibitors of apoptotic protein (XIAP), and survivin. Several studies show that resveratrol enhanced TMZ toxicity by the generation of reactive oxygen species (ROS), activation of AMPK signaling, inhibition of mTOR pathway, and reduced the activity of antiapoptotic factor Bcl-2 in SHG44 GBM cells. In addition, the synergistic therapy of resveratrol with TMZ reduced the orthotopic xenograft growth of GBM cells (Yuan et al. 2012).

- **Cucurbitacin.**

The Cucurbitacins are obtained from the Cucurbitaceae family isolated naturally from plants and are chemically terpene sterols. They are further classified into 12 major classes (Jian et al. 2005). Out of 12 classes, cucurbitacins I, E, B, D, and Q are well known for their anticancerous activity in various cell cultures or cell lines. The anticancer activity of cucurbitacins involved in halting the cell cycle and lead to programmed cell death by blocking the Janus kinase/Signal Transducer Activator of Transcription 3 (JAK/STAT3) pathways. It was observed that cucurbitacin B stimulated the division and colonization of U87 colonies and T98G GBM cells. In addition, cucurbitacin B also shows the disruption of the myo and microtubular networks, leading to the loss of cell migration, thus, preventing cell entry and its proliferation (D. Yin et al. 2008).

- **Betulinic acid.**

The Betulinic acid (BetA) is isolated from the birch trees (*Betula pubescens*) and selfheal (*Prunella vulgaris*). It is very well known for its several properties involving antimalarial, anti-inflammatory, and anti-retroviral. Various latest evidence has shown their effective cancer-protective properties in many human tumors or cancers with no visible action on healthy cells (Kessler et al. 2007). Furthermore, it has been observed that cell death in human neuroblastoma cells in in vitro and in vivo models. Also, by induction of a p53 independent caspase–PARP cascade and BetA activates cell death in five different cancerous cell lines. BetA has an important role in the induction of cell death which was linked with the raised concentrations of the pro-apoptotic protein Bax, formation of ROS, and DNA fragmentation. Similarly, BetA encouraged cell death was also reported in brain cancer cells in in vitro studies (Fulda et al. 1999).

- **Xanthones and Lactones.**

Xanthones possesses well-evidenced cancer-protective activities, antimicrobial and anti-inflammatory properties. The Cudraxanthone-I xanthone was isolated from Milicia excels which suppressed the differentiation and growth of the U87 and act as the resistance of U87 EGFRvIII GBM cell lines (Kuete et al. 2014). The Lactones are resultant of *Vernonia cinerea* (little ironweed or ash fleabane), belongs to the

Asteraceae family which have antimalarial, anti-inflammatory, and anti-metastatic properties (Pratheeshkumar & Kuttan 2011). The Sesquiterpene lactones are majorly obtained from *Vernonia cinerea* which truly suppresses the STAT3 function in U251 GBM cells and hence, reduces their livelihood, and suggests anticancerous properties.

- **Rutin.**

The vascular endothelial growth factor (VEGF) and transforming growth factor-β1 (TGF-β1), both affect the GBM cell growth, progression, angiogenesis, and proliferation. Rutin, a very well-known flavonoid obtained from the seeds of *Dimorphandra mollis*, is also known as fav era. On other hand, rutin suppresses the release of both VEGF and TGF-β1 in GBM GL-15 cells and thus, results in the inhibition of angiogenesis and chemoradiotherapy (CRT) resistance. It is significantly demonstrated that the anti-VEGF antibody bevacizumab inhibits the production of VEGF but no effects were observed on the expression or production of TGF-β1 [155]. Rutin is also very well known to inhibit skin cancers (Freitas et al. 2011).

Current Status of Natural Products on On-Going Clinical Trials in TBI

Sr. No.	Treatment	Status	ClinicalTrials.gov Identifier
1	MLC901[a]	Not yet recruiting	NCT04766281
2	Hemp-derived CBD and other cannabinoids	Withdrawn (lack of initial funding after approval of study)	NCT03826368
3	Sunflower and medium chain triglyceride oils	Completed	NCT02723344
4	OLIGOPIN[b]	Completed	NCT03777683
5	EGCG (epigallocatechin −3-gallate)	Completed	NCT02731495

aMLC901 was originated from Traditional Chinese medicine which combines nine herbal components (including *Radix astragali, Radix salviae miltiorrhizae, Radix paeoniae rubra, Rhizoma chuanxiong, Radix angelicae sinensis, Carthamus tinctorius, Prunus persica, Radix polygalae,* and *Rhizoma acori tatarinowii*) and five animal components (including *Hirudo, Eupolyphaga seu steleophaga, Calculus bovisartifactus, Buthus martensii,* and *Cornu saigae tataricae*) (Tan et al. 2020)
bOLIGOPIN is an extract of French maritime pine bark extract (Majidi et al. 2021)

Conclusion

Brain tumors can be categorized into a wider range of cancers, each having different initiating factors, progression, proliferation, and spreads into different tissues or specific parts of the body. The present focus of cancer research is on the molecular basis and identification of different phytochemicals with their pro- and

anticarcinogenic potential. There are a number of plant products and their secondary metabolites which could prove a beneficial ray of hope in the field of oncology. Cancers portray serious challenges in the developing nation. Thus, there is a strong urge to understand the molecular basis of causes and to develop effective and novel delivery techniques of newer therapeutics with lesser side effects. Nevertheless, this chapter helps to improve the understanding of the pathology of brain cancers and suggests possible new therapeutic targets mainly focused the field of phytochemicals with the primary targets of improving the care and treatment of cancer patients.

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