



(REVIEW ARTICLE)



## A review on nutraceuticals: A healthy way to treat brain cancer

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GSC Biological and Pharmaceutical Sciences, 2021, 15 (03), 335–348

Publication history: Received on 28 May 2021; revised on 02 July 2021; accepted on 04 July 2021

Article DOI: <https://doi.org/10.30574/gscbps.2021.15.3.0186>

### Abstract

A Balanced body is important for good health and for balancing the state of body, healthy food is necessary. Cancer is the uncontrolled growth of cells which upon time worsen and turns into tumor and as it is a leading cause of death worldwide, it is so important to research and find alternative treatments for the management of cancer. Nutraceuticals are known as alternative approach for the control of cancer. Nutraceuticals has many health benefits, and now known as the future of treatment for various health diseases. It has shown to elicit anti-aging, anti-cancer and other health enhancing effects. Nutraceuticals also have significant promise in the promotion of human health and disease prevention. Since, the present cancer treatment has various side effects, the benefits of these nutraceuticals may result in approaches to improve human health in a alternate way. In this review, we highlighted the etiology, diagnosis, pathogenesis of brain cancer along with treatment by using nutraceuticals.

**Keywords:** Glioblastoma; Sulforaphane; Curcumin; Nutraceuticals; Brain cancer

### 1. Introduction

Brain cancer is a tumor that starts and stays in the brain, e.g., Gliomas. It can be classed as either benign or aggressive brain cancer. Benign brain cancer is a type of cancer that seldom spreads and invades surrounding tissues, has definite borders, and slow-growing cells. Pituitary Tumors, meningiomas, and astrocytomas are examples of benign brain Tumors, but malignant brain cancer spreads quickly across the brain and spinal cord, has no apparent borders, and has fast developing cells. High-grade astrocytomas, oligodendrogliomas, and other malignant types of brain cancer are examples [1]. Brain cancers impose a highly devastating impact on the health of the patients [2]. Annually, 321000 cases of brain and nervous system cancer are reported, with a mortality rate of 229000. Unfortunately, cancer incidences were seen not only in adults, but also in children aged 0 to 19 years [1] Because the blood-brain barrier (BBB) makes it difficult to acquire therapeutic levels of medications in neural brain tissues, therapies for the treatment and cure of brain malignancies are being developed [2]. Deregulation of signaling pathways results in uncontrolled cellular proliferation, metastatic transformation, and invasion in brain tumors due to complex genetic and epigenetic changes [3]. Radiotherapy, surgical procedures, and chemotherapy are all used in the treatment of brain cancer [1,4,5]. Furthermore, greater relapse rates and a poor prognosis in brain malignancies exacerbate the situation, resulting in a high mortality rate [6,2,7]. Nausea, exhaustion, dehydration, a lower WBC count, hair loss, and other adverse effects are common in radiotherapy and chemotherapy [8,9,10]

Nutraceuticals, according to Stephen DeFelice, are a combination of nutrients and pharmaceuticals that have a potential application in health issues [11]. A nutraceutical is a food extract supplement that has been scientifically demonstrated to provide health benefits in the treatment and prevention of disease. Nutraceuticals include everything from isolated nutrients, nutritional supplements, and diets to genetically modified “designer” foods and herbal supplements [2].

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Nutraceuticals have anti-aging [13], anti-inflammatory [14], and antioxidant [15], and anti-cancer effects, among others [16].

Plant products and nutraceuticals may be a cost-effective way to prevent cancer, according to emerging evidence from a variety of studies [17,18]. Some dietary supplements may be beneficial in cancer, according to nutritional biochemistry [19]. The growing relevance of naturally occurring phytochemicals in plants for use in the prevention of human diseases, including cancer, has been facilitated by a rapid increase in the cost of health care, combined with the limited effectiveness of single target cancer treatment therapies, in the last decade [20]. Because of their capacity to lower the risk of adverse effects produced by chemotherapy, nutraceuticals have promise in combinatorial clinical cancer therapies [21,22]. This study aims to bring together all of the well-known main nutraceuticals that have been shown to be effective against brain cancer, as well as their putative action mechanisms, as well as in vitro and animal research on their potential in brain cancer treatment. Nutraceuticals provide a fresh potential for pharmacological applications, according to the review, and these entities could serve as an appealing scaffold for drug development against brain cancers. As a result, this allowance would enable ordinary people to choose more desirable nutraceuticals in addition to traditional neuroprotective medicines to treat brain cancer and enhance lifestyle patterns [23].

### 1.1. Etiology

Two major risk factors associated with the occurrence of brain cancer are either environmental or genetic.

- Environmental factors include: Ionizing irradiation of brain is recognised exogenous risk factor [24,25,26], cigarette smoking, excessive alcohol consumption, poor diet, lack of exercise, excessive sunlight exposure, sexual behaviour that increases exposure to certain viruses, consuming cured food, previous medical history of epilepsy, head trauma, seizures, exposure to various types of pollutions, administration of medicines like sleeping pills, over the counter drugs, anti-histaminic drugs and wide exposure to industrial harmful chemicals.
- Genetic factors include gene mutations in bodily cells, aberrant hormone levels in the blood, a weaker immune system, and carcinogen exposure [1].

### 1.2. Symptoms

Memory problems, seizures, changes in speech, hearing or vision problems, changes in behavior, increased intracranial pressure causing headaches, nausea, vomiting, drowsiness, weakness on one side of the body, strange feeling in head, and strange smells, loss of consciousness and general irritability, depression or personality changes [1], gait imbalance, seizures, aphasia, urinary incontinence and Hemiparesis [27], papilledema [5] are some of the symptoms that a person with brain cancer may experience.

### 1.3. Diagnosis

The following test parameters are used to make a diagnosis of brain cancer:

Examination of the Nervous System: Vision, hearing, awareness, muscle strength, coordination, and reflexes are all checked during a neurological examination. Different imaging modalities, like as Computed tomography scans and Magnetic Resonance Imaging scans are used to confirm the presence of a brain tumor, followed by a neurological evaluation. Other approaches for identifying brain cancer, in addition to image scanning, include

#### 1.3.1. Cerebral angiography and MRI angiography (MRA)

These tests employ x-rays and iodine-containing contrast material to create an image of blood vessels in the brain, as well as provide further information on abnormalities detected by CT or MRI scans of the head. The use of angiography for brain tumors is to plan the surgical removal of a tumor suspected of having a large blood supply due to abundant of blood vessels [1]. The majority of malignant glioma tumors have spread more than 15 mm over the area that may be seen on an MRI scan [28,29].

#### 1.3.2. Magnetic Resonance Spectroscopy (MRS)

MRS exposes the chemical makeup of the brain and can be used to diagnose low-grade gliomas and Tumors with a lot of edemas around them. This method can also help distinguish between tumor recurrence and radiation necrosis.

Single photon emission computerized tomography (SPECT or SPET) scan. This technique produces 3D images of the body in order to monitor blood flow in the brain, as higher blood flow rates are predicted in the event of brain cancer.

### 1.3.3. Biopsy

This method is used to examine the disease. Needle biopsy and stereotactic biopsy are two types of biopsies. A neurosurgeon drills a small hole in the skull and inserts a narrow, hollow needle into the Tumor, removing and examining a sample of the Tumor via the needle's core. Stereotactic biopsy is a sort of needle biopsy that locates the Tumor with the help of a computer and a three-dimensional scanning instrument.

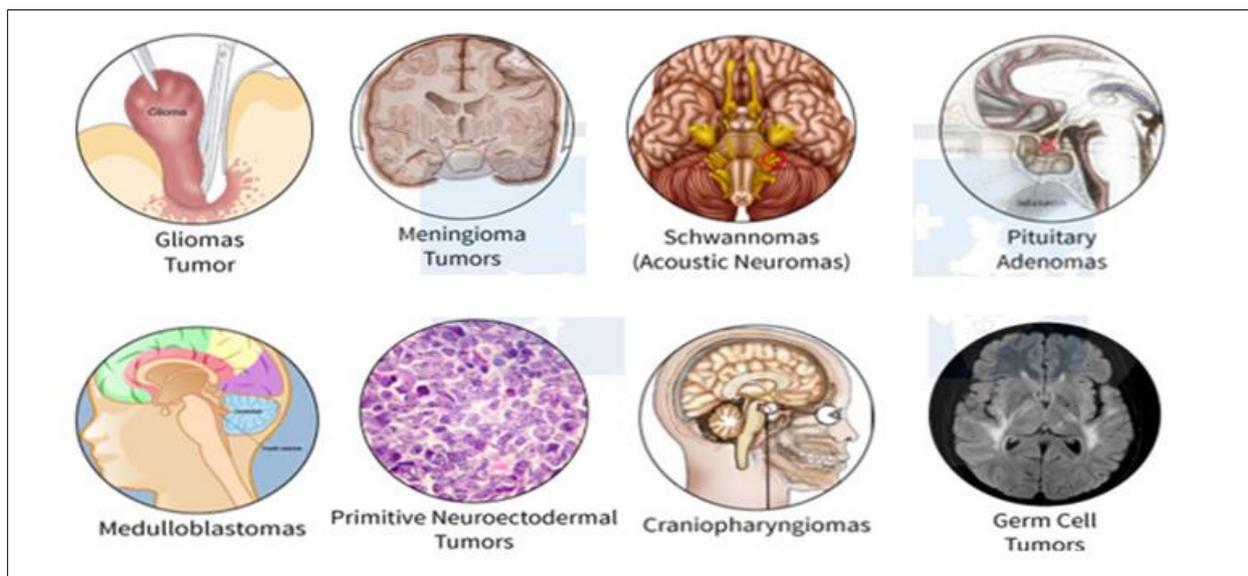
### 1.3.4. PET

PET stands for positron emission tomography, a type of imaging that uses a few radiotracers to diagnose and assess disease severity. It aids in the differentiation of Tumors, radiation necrosis, and normal brain. The combination of CT and PET scans reveals the anatomy (from the CT scan) and functions (from the PET scan) of the brain [10,30,31].

## 2. Types and pathogenesis of brain cancer

Brain cancer is an extremely fatal disease that affects both the elderly and youngsters alike [2]. Because of their aggressive nature and limited therapeutic choices, metastatic brain Tumors are among the most lethal human malignancies [3]. Gliomas [7,1], glioblastomas [32,1,5], meningioma [33], medulloblastoma [33,34], pituitary adenoma [35], schwannomas [36], craniopharyngioma, and germ cell Tumor are examples of malignancies [Figure 1]. Gliomas and glioblastomas are the two most aggressive kinds of brain cancer, and their significantly expanding prevalence and burden represent a huge medical challenge [1].

Adults with gliomas have the most prevalent primary malignant brain Tumors. They can appear anywhere in the central nervous system, but they most commonly do so in the brain, where they form in glial tissue [4]. Men are more likely than women to have gliomas, and white people are more likely than black people to develop them [27]. Glioblastomas and other malignant gliomas account for over 75% of all malignant brain Tumors [37]. Glioblastoma multiforme (GBM), a class IV neoplasm with astrocytic differentiation, is the most frequent malignant Tumor of the CNS, even more prevalent than CNS metastasis, according to the World Health Organization (WHO) classification of malignancies of the central nervous system (CNS) [38-41]. Glioblastoma (grade IV) is the most aggressive of all the subtypes of primary brain gliomas and has the worst prognosis, even after surgical resection combined with radiation and/or chemotherapy [42].



**Figure 1** Types of brain cancer

**Source:** blkhospitals.wordpress.com

The most common and malignant brain Tumor in adults is glioblastoma [43]. Glioblastoma is most commonly found in the deep white matter of the cerebral hemispheres [44], with the frontal lobe being the most common location [5]. Glioblastoma is the most common type of malignant glioma, accounting for 82 percent of cases. It has a high level of cellularity and mitotic activity, as well as vascular growth and necrosis. Glioblastomas were once known as glioblastoma

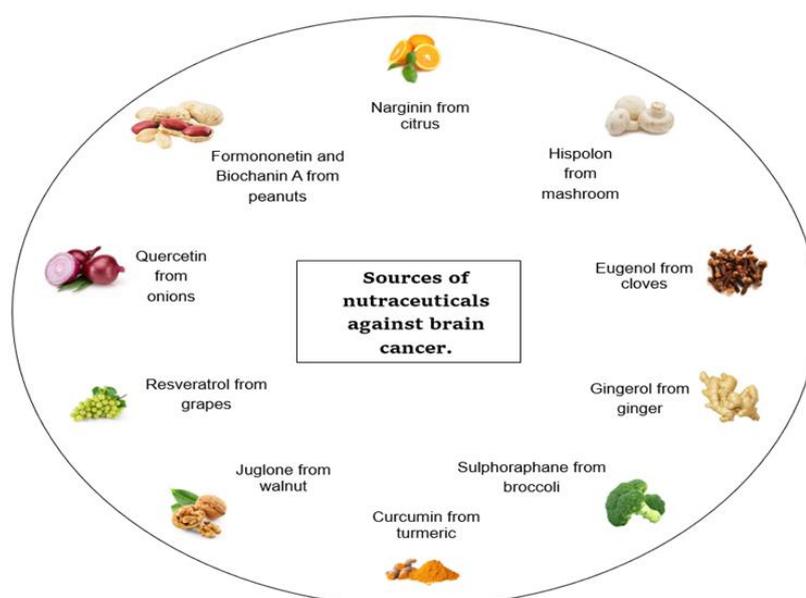
multiforme because the cells in these Tumors vary in size and shape, or are pleomorphic [45]. It has aggressive proliferation of normal brain tissues as well as increased angiogenesis [41,46]. Furthermore, progression to glioblastoma involves amplification of the Epidermal Growth Factor Receptor (EGFR) gene and the expression of angiogenic factors such as vascular endothelial growth factor (VEGF) [47,48,5], increase the p53 degradation [3]. NF1 mutation/deletion is common in the mesenchymal subtype, as is increased expression of CHI3L1 and genes implicated in the Tumor necrosis factor and nuclear factor- $\kappa$ B pathways [49,50,27].

Pin1 is a peptidylprolyl isomerase (PPIase) that catalyses the isomerization of phospho-serine/threonine and proline peptide bonds [51,52]. In human GBM specimens, the expression of the Pin1 protein was increased [53,54]. As a result, it's critical to see if Pin1 inhibitors can be used as a chemotherapeutic in this condition [55]. Glioblastomas have pleomorphic cellular populations and are histologically similar to anaplastic astrocytoma [56]. Glioblastomas are difficult to treat because of their location and complex heterogeneous biology [57]. Radiotherapy, surgical resection, and temozolomide therapy are all used to treat these malignancies [58]. Lymphoma, nausea and vomiting, hepatitis B reactivation, and rashes are all common side effects of temozolomide therapy [27], as are mouth ulcers, changes in taste, coughing, constipation, and exhaustion.

### 3. Management

Anti-cancer properties of nutraceuticals and alternative medicine have been extensively researched. Nutraceuticals can be utilised at large doses or as an adjuvant to chemotherapy because of their low toxicity profiles [59]. Nutraceuticals can significantly induce the production of cytokines such as Tumor necrosis factor, interferons, and interleukins, and potentially activate natural killer cells, T lymphocytes, and macrophages in cancer patients in their late stages, including decreased activity of natural killer (NK) cells and cytokine production [60]. Because the blood–brain barrier (BBB) prevents medicines from sustaining therapeutic levels within the brain, there are no medications available to address brain cancer [2].

The ability of nutraceuticals to traverse the BBB confirms their anti-cancer potential [61]. Dietary habits have continuously been demonstrated to be one of the most important determinants of cancer, neurological illnesses, cardiovascular diseases, and type II diabetes in epidemiological research. Dietary habits and food choices have a direct impact on health and disease [22]. Curcumin from turmeric, naringin from citrus, eugenol from cloves, gingerol from ginger, juglone from walnuts, formononetin and biochanin A from peanuts, quercetin from onions, Resveratrol from grapes, sulforaphane from broccoli, and Hispolon from mushroom have all been found to have anti-brain cancer properties [Figure 2].



**Figure 2** Sources of nutraceuticals against brain cancer

**Source:** <https://Novapublishers.com/shop/bioactive-nutraceuticals-for-brain-disorders>

### 3.1. Curcumin

Curcumin is a yellow pigment derived from the turmeric spice *Curcuma longa*. Curcumin is currently available in the form of beverages, tablets, capsules, lotions, gels, nasal sprays, extracts, and colouring additives for both edible and medical purposes, thanks to its significant characteristics [62]. Curcumin has been used to cure a variety of diseases in ancient Chinese and traditional Indian medicine. Curcumin has been used for medical purposes since the Unani and Vedic eras. [20]. Curcumin has various chemical qualities that are advantageous to health, including antioxidant, anti-inflammatory, and chemotherapeutic potential [59,62]. Curcumin has a minor cytotoxic effect on the C6 cell line of glioma [63]. In human glioma cell lines, curcumin therapy suppressed NF- $\kappa$ B and MMP and caused TRAIL-dependent apoptosis [64]. Curcumin stimulates NF- $\kappa$ B activation in C6 cells, which is blocked by paclitaxel and curcumin. The two medications together elevated p53 and p21 levels even more, boosting the antiproliferative effects. Furthermore, paclitaxel plus curcumin significantly increased the activation of caspase-3, an apoptosis pathway effector, while decreasing the expression of the anti-apoptotic protein Bcl-2. The gene that controls transcription Oncogenesis, Tumor development, and treatment resistance are all controlled by NF- $\kappa$ B in various types of cancers [65].

Curcumin has antiproliferative effect against the DAOY cell line after crossing the blood-brain barrier. Curcumin enhances apoptosis through altering the Shh (sonic hedgehog) pathway, which regulates the balance between cell death and proliferation [66]. Curcumin's antitumoral properties are assumed to be mediated by a variety of signaling pathways, including cellular proliferation, apoptosis, autophagy, angiogenesis, immunomodulation, invasion, and metastasis [67,59]. Curcumin can cause G2/M cell cycle arrest and death [59,20], as well as upregulate p53 expression and promote p21WAF-1/CIP-1 expression [20]. Curcumin may improve the radiosensitivity of human glioma U87 cells by promoting G2/M phase arrest by upregulating DUSP-2 expression and inhibiting phosphorylation of ERK and JNK (c-Jun N terminal kinase) [68].

### 3.2. Naringin

Grapes and citrus fruits contain a flavanone glycoside called naringin. It has a unique grapefruit juice bitterness to it [69]. Naringin has a wide range of therapeutic effects, including anti-cancer [70,71], anti-oxidant [72], anti-inflammatory [71], and neuroprotective properties [73,70]. Naringin has been shown to have anti-cancer properties in a variety of malignancies, including glioblastoma, breast, colon, and lung cancers [74]. FAK is a tyrosine kinase that is essential for cell survival and proliferation [75]. Survival, motility, metastasis, angiogenesis, and the epithelial to mesenchymal transition (EMT) are all important functions of FAK [76-79]. Because FAK is overexpressed in glioblastoma, a small molecule inhibitor of FAK autophosphorylation can significantly reduce the development of glioblastoma cells [80]. Naringin inhibits human glioblastoma cell metastasis by inactivating the p38 signaling pathway [81]. Naringin has been shown to inhibit the PI3K/AKT, c-Myc, and c-Src pathways [82]. FAK activity could be inhibited by Naringin. The glioblastoma cell U87 MG was successfully suppressed by Naringin. Naringin inhibits U87 MG cell metastasis by blocking Matrix Metalloproteinases. Naringin inhibited the downstream of FAK to regulate the biological function of the U87 MG cell by targeting FAKp-Try397. By influencing the apoptotic cascade and activating caspase-3, Naringin can increase apoptosis in U87 MG cells [81].

### 3.3. Eugenol

Eugenol is a phenolic natural chemical that is the active ingredient in clove and is used to treat cancer [83]. The major component of cloves is eugenol, and its isomer isoeugenol is made from eugenol by a natural process in cloves. These compounds are employed as flavouring ingredients in non-alcoholic drinks, baked foods, and chewing gum, and are included into a number of dental materials as well as household and personal hygiene items such as fragrances, cream lotions, soaps, and detergents [84]. Eugenol inhibits growth and proliferation while also inducing apoptosis by targeting the E2F1/surviving pathway [22]. Antifungal, anti-inflammatory, antiseptic, anaesthetic, and anti-cancer properties are among the biological actions of eugenol. Eugenol raises the quantities of free calcium (Ca<sup>2+</sup>) ions in the cytoplasm of glioblastoma DBTRG-05MG cells. Apoptosis is promoted by increasing Reactive Oxygen Species generation, cytochrome c discharge, activating caspase-9 and caspase-3, and decreasing Matrix metalloproteinase [85].

### 3.4. Gingerol

The rhizome's main bioactive ingredient, gingerol (6-GN), is responsible for the pungency [86]. Gingerol is well-known for its contribution to human health and nutrition, and it has a wide range of biological activities, including anticancer, anti-oxidant, antibacterial, anti-inflammatory, and anti-allergic properties, as well as actions involving the central nervous system [87]. Gingerol Proliferation and metastasis were inhibited, cell cycle arrest was achieved by inhibiting Akt and p38MAPK activity, and epidermal growth factor receptor expression was decreased [88]. The human glioblastoma U87 cell line responds to gingerol by becoming cytotoxic. It is known to make TRAIL more sensitive. TRAIL, a member of the Tumor necrosis factor (TNF) family, can cause apoptosis when it interacts with DR4 and DR5 (death

receptor-4, -5). TRAIL-related apoptosis can be triggered by a variety of synthetic and natural compounds [89]. Gingerol binds to TRAIL and stabilizes the average ratio of proapoptotic (survivin, Bax) to antiapoptotic (Bcl-2) proteins in U87 cells, resulting in apoptosis. Furthermore, gingerol-induced ROS levels resulted in PARP-1 (Poly (ADP-ribose) polymerase) breakage, which triggered apoptosis [90].

### 3.5. Juglone

Juglone is a brownish yellow naphthoquinone that belongs to the phenolic compounds subclass. It was isolated from the walnut tree [91]. Juglone, a Pin1 inhibitor, inhibits proliferation, increases caspase 3 activity, promotes apoptosis, and reduces migration in U251 glioma cells, as well as inhibiting angiogenesis by blocking VEGF (vascular endothelial growth factor). Juglone's anticancer processes were linked to Pin1 downregulation and inhibition of downstream signaling pathways such as TGF-1, Smad2/3, and miR-21, implying that Pin1 inhibition could be a promising treatment target for glioma. Juglone reduces Tumor cell development by a variety of mechanisms, including cytotoxicity, apoptosis induction, and angiogenesis avoidance [55]. Juglone has also been shown to inhibit the growth of glioblastoma cells by increasing ROS levels and activating the p38-MAPK pathways [92].

### 3.6. Formononetin

Formononetin is a non-steroidal bioactive polyphenol found in a wide range of plants [93]. Formononetin, which is derived from soy beans and red clover, is known to have a variety of pharmacological properties, including anticancer [94], anti-inflammatory [95], and antioxidant properties [96]. Formononetin inhibits cancer growth by triggering apoptosis, interrupting the cell cycle, and preventing metastasis by targeting a variety of pathways that are commonly mutated in diverse malignancies [97]. Formononetin has the ability to stop the proliferation of C6 glioblastoma cells, but when combined with temozolomide, it has a stronger effect on C6 cell growth. When these two medicines were combined, they triggered apoptosis by increasing the Bax/Bcl-2 proportion, resulting in caspase 3 and 9 breakage. In C6 cells, formononetin was also found to cause apoptosis by inhibiting the expression of Matrix Metalloproteinase (MMP) 2 and 9 [98].

### 3.7. Biochanin A

Biochanin A, also known as O-methylated isoflavone, is a phytoestrogen-like natural chemical molecule. It's mostly present in legume plants like *Trifolium pratense* [99], and it's mostly isolated from soya products like chickpeas. Chickpea is a legume that is eaten by humans as a source of nutrition [100]. Biochanin A has been proven in a number of studies to offer health benefits, including the prevention of malignancies, heart disease, menopausal symptoms, and osteoporosis [101,99], as well as anti-inflammatory and antioxidant properties [102,103]. Reactive oxygen species and other invading enzymes are also protected [104]. Biochanin A, a DNA repair inhibitor, enhances the lethal effect of temozolomide in human glioblastoma cells, U-87 MG, by reducing cell proliferation and modifying cell metabolism. In human glioma U87MG cells, biochanin A causes G2/M phase arrest. However, when taken in combination with temozolomide, this chemical increased the potential activity of temozolomide by inhibiting growth in the G1 phase of the U87MG cells. Temozolomide and biochanin A (alone and in combination) inhibited the expression of cell signaling proteins such as ERK, p-ERK, AKT, p-AKT, EGFR, and c-myc while increasing the expression of phosphorylated-p53 (p-p53) [102]. Biochanin A reduced the enzymatic ability of MMP-9, which reduced the percentage of U-87 MG cells in a dose-dependent manner [105].

### 3.8. Quercetin

Quercetin is a flavonoid found in foods including onions, red wine, green tea, and apples [106], as well as cabbage, tomatoes, parsley, pears, plums, cherries, strawberries, blueberries, and cranberries. Capers, elderberries, and lovage leaves are the best sources of quercetin [107]. Anti-inflammatory, antibacterial, antiviral, antiplatelet, and anti-proliferative properties have also been found for quercetin [108]. Quercetin decreases cytokine synthesis in the lungs and brain by scavenging ROS, and thereby reduces inflammation [107]. Quercetin promoted apoptosis, ER stress, pSTAT3/Bcl2 axis activation, and protective autophagy [22].

Quercetin increased glioma cell apoptosis by stimulating caspase 3 activity and decreasing expression of survivin, an antiapoptotic protein, decreased cell proliferation and viability, arrested the cell cycle [107]. Quercetin is a potent antioxidant because of its ability to scavenge free radicals and bind transition metal ions. It's worth noting that quercetin can effectively limit glioblastoma cell growth and induce apoptosis by reducing the NF-B, Ras/MAPK/ERK, and PI3K/AKT signaling pathways, with AKT being responsible for cell viability reduction. The Bcl-2 family includes two major members, Bax and Bcl-2, both of which play important roles in Tumor growth [108]. In response to various physiological stressors, Bax, a pro-apoptotic protein, promotes cell death by permeabilizing the mitochondrial outer membrane. Bcl-2, on the other hand, is a crucial anti-apoptotic component that prevents apoptosis by reducing Bax

activity [109]. Quercetin caused apoptosis by inhibiting the production of apoptotic genes such as Bax and Bcl-2, as well as stopping the cell cycle in the G2/M phase. Glioblastoma U251 cells are inhibited by quercetin in a dose-dependent manner. U251 cell migration and invasion were dramatically reduced after quercetin therapy. Matrix metalloproteinase (MMP9 and MMP2) are metalloproteinases involved in cell migration. Quercetin decreased glioblastoma cell motility and angiogenesis by lowering VEGFA, MMP2, and MMP9 expression [108].

### 3.9. Resveratrol

Resveratrol (RES) is a stilbenoid phenol produced by a variety of plants (most commonly found in the skin of berries like grapes, blueberries, and raspberries) that has promising and strong effects on a variety of human health issues [22]. This polyphenol regulates biological functions such as cell proliferation, cell division, apoptosis, angiogenesis, and metastasis, providing chemo preventive and therapeutic actions in many cancers [106]. Resveratrol can reduce angiogenic and metastatic rates by inhibiting COX-1 and COX-2, as well as other related proteins implicated in cancer progression. They have antioxidant characteristics that directly scavenge ROS [22] and resveratrol also acts as a neuroprotective agent, inhibiting the creation of new blood vessels [110]. Resveratrol decreased glioblastoma growth by inhibiting GBM growth and invasion, partially through AKT deactivation and p53 induction [111]. A S-G2/M phase arrest was caused by resveratrol [112]. The application of resveratrol inhibited the Hypoxia-inducible factor HIF-1 in the glioma cell line U87 MG. The ability to generate U87 cancer cell colonies was reduced when resveratrol and iododeoxyuridine were combined [113]. Resveratrol's effects on the activation of autophagy and apoptosis in glioblastoma cells. After resveratrol therapy, autophagy protein 5 (Atg5), beclin-1, and Microtubule-associated proteins 1A/1B light chain 3B [LC3-II] were raised in three GBM cell lines, indicating that it enhanced autophagosome formation. The effects of RES on primary human glioblastoma cells and human U87MG cells. It inhibited invasive growth while promoting differentiation [16].

### 3.10. Sulforaphane

Due to its promise health-promoting qualities in disease and low toxicity in normal tissue, sulforaphane (SFN), an isothiocyanate (ITC) produced from cruciferous vegetables, particularly broccoli and broccoli sprouts, has been widely explored [32]. Sulforaphane has been shown to have anti-cancer effects [114]. Anti-inflammatory, antibacterial, and antioxidant properties are all present in this molecule. Sulforaphane is a strong chemo preventive and antitumoral natural agent in cancer cells [106,115]. After i.p. injection, sulforaphane can quickly cross the BBB and accumulate in the CNS. When examining the possible impact of these chemicals on human health, bioavailability and metabolism of sulforaphane are important considerations [32]. It has been extensively researched due to its minimal toxicity to normal cells and high bioavailability [32,116]. It is quickly absorbed, processed, and eliminated, with 80 percent of it showing in the urine within 12–24 hours of consumption or injection, indicating high bioavailability [115]. In the therapy of GBM, sulforaphane has anti-apoptotic, anti-invasion, anti-proliferative, and anti-chemo/radio resistance properties [32].

Sulforaphane inhibits the growth of U251MG glioblastoma cells and induces apoptosis. Increased expression of Bad, Bax, and cytochrome C were associated with apoptosis induction, while antiapoptotic proteins Bcl-2 and survivin were reduced. Because these Metallo proteinases are responsible for cell migration, the inhibition of invasion was followed by increased E-cadherin expression and decreased expression of MMP-2 and MMP-9 [117]. In U373MG and U87MG cells, sulforaphane inhibits cell proliferation. Sulforaphane raises the amount of ERK1/2, which regulates several processes through phosphorylation and activation of ERK and Bax. Caspases-3 activity was elevated by sulforaphane, which accelerated apoptosis [118]. Sulforaphane and temozolomide suppressed NF-B in a synergistic manner, increasing glioblastoma chemosensitivity [119]. Glioblastoma cells T98G and U87MG are affected by sulforaphane. Activation of caspases-12 and-9, increased Bax expression, and decreased Bcl-2 antiapoptotic protein resulted in an apoptotic impact [120].

Immunotherapy has emerged as a viable treatment option for glioblastoma patients [121], but immunosuppression, both local and systemic, has proven to be a significant barrier to effective immunotherapy. The function of immunoregulatory lymphocytes in glioma-related cellular immunity suppression, as well as putative tumor-specific mechanisms. In many immunologic systems, these cells have been progressively identified as the key controllers of the cellular immune response [122]. This study aims to alleviate immunosuppression in glioblastoma patients by blocking monocytes' conversion to immunosuppressive leukocytes using sulforaphane at pharmacologically safe amounts for normal leukocytes [123].

### 3.11. Hispolon

Hispolon a yellow pigment polyphenolic molecule derived from *P. Linteus* mushrooms [124,125] exhibits anti-inflammatory, antimetastatic, and antiproliferative properties, as well as immunomodulatory properties [126].

Glioblastoma cells from the U87MG strain are resistant to Hispolon. Depending on the cell environment, the G2/M phase occurs [125]. In U87MG cells, Hispolon causes cell cycle arrest in the G2/M phase. GBM cell growth is inhibited by Hispolon, which causes apoptosis. In U87MG, it also increased caspase 3 activity. The concentration of cyclin D4 was reduced during the hispolon treatment, which was accompanied by a rise in the CDK inhibitor protein, p21. The increase in p53 levels resulted in apoptosis [124].

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#### 4. Conclusion

Since, the treatment of brain cancer is very complicated and challenging, Nutraceuticals being a food source, proved helpful in the treatment of brain cancer and also has many health benefits. It is currently known as future of treatment for various diseases and ailments. Nutraceuticals are well known for their neuroprotective and healing properties, so consuming them in recommended and acceptable doses promotes good health and helps in treating brain cancer. Further studies on nutraceuticals are going on in managing other diseases. We hope studies which are currently in research and development process will be helpful in near future and provide positive results in the treatment of diseases.

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#### Compliance with ethical standards

##### *Disclosure of conflict of interest*

No conflict of interest.

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