Chapter-9

Intricacy of Hypoxia Signaling in Glioblastoma and its Consequences for Therapeutic Intervention

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Abstract

Background: Glioblastoma (GBM) is a common occurring malignant tumor in the brain and it is classified as grade IV astrocytoma. Hypoxia-inducible factor 1α (HIF-1α) has considered a crucial factor activated by hypoxia in the pathogenesis of GBM. A deficiency of oxygen in body tissue or hypoxia causes hyper-vascularization and necrosis. HIF-1α stimulates tumor progression through the activation of immunosuppression, metabolic reprogramming and angiogenesis leading to cell invasion and survival in aggressive and high-grade gliomas. Oncogenic signaling pathways such as PI3K-PTEN, ERK-MAPK has reported to be modulated by hypoxia in GBM. Most of the clinical intervention of GBM has limited by its side effects and induced neurotoxicity in brain. Herbal compounds such as curcumin, bacoside, ellagic acid, astaxanthin, ashwagandha etc., have attracted much of interest to target the aberrant signaling pathways or protein implicated in GBM.

Objective: The objective of this study was to dissect the role of hypoxia signaling in GBM and its consequences for therapeutic intervention in light of recent updates.

Method: PubMed databases, Google Scholar and carried out a literature review on the contribution and effective role of signaling pathways and herbal compounds in the pathogenesis of GBM.

Result & Conclusion: The intricate relationship between HIF-1 and GBM underscores its significance in influencing key processes associated with the development and progression of this aggressive brain tumor. Many Indian traditional herbs have the potential therapeutic properties against glioblastoma. Therefore, inhibiting the aberrant pathway through herbal compounds could be a potential alternative treatment for this disease.

Keywords: GBM, hypoxia, HIF-1α, herbal compound, signaling pathways.

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1. INTRODUCTION

Glioblastoma (GBM) is most common and highly intrusive malignant brain tumor and WHO has classified it as a Grade IV tumor. It has a median survival of 1-1.5 year and has an annual mortality of around 13000 lives in the U.S. alone [1-6]. It was identified by Rudolf Virchow in 1863 as a form of glioma. GBM is a subtype of gliomas, tumor originating from precursor & glial cells, which encompass oligodendrogliomas, ependymomas and astrocytomas. Although it is known as rare, having an incidence rate of 5 cases per 1,00,000 people, GBM constitutes around 14.5% of all brain and CNS tumor. Approximately 48.6% of glioblastoma are malignant tumor. As per Central Brain Tumor Registry of the United States database, males of a median age 65 are mostly affected by it and exhibit a five-year survival rate of around 6.8%, where it depends on the patient characteristics and histology of tumor [7]. The estimated percentage change in the 5-year survival rate for brain tumor has reported about 2.3%, while all cancers together showed an 18.3% enhancement [8,9]. However, as per the Global Cancer Statistics for the year 2020, CNS tumor accounted for 1.6% of newly diagnosed cancer cases worldwide. Gliomas have identified as the predominant primary CNS tumor, comprising approximately 75% of these cases. The annual incidence of gliomas displayed variations, with rates reported as 7.3 per 1 lakh individuals in the USA between 2007 and 2016, 7.47 per 1 lakh people in Korea during the same period, while around 8 per 1 lakh individuals in China from 2016 to 2022 [138,139]. The temporal and frontal lobes of cerebral hemispheres are the main sites for GBM while a small percentage also occurs in the brainstem, spinal cord, and cerebellum [10]. Apart from primary GBMs some secondary tumor, develop from low-grade astrocytomas, are also found [11]. Furthermore, GBM is classified into 4 subtypes i.e. classical, neural, proneural, and mesenchymal.

WHO classified GBM as Isocitrate dehydrogenase 1 (IDH1) wild-type (IDH1wt) [12]. This form is the most widespread and destructive form in all primary malignant brain tumor. IDH1 is a protein present in the cytoplasm, endoplasmic reticulum (ER), and peroxisomes. During oxidative decarboxylation of isocitrate into α-ketoglutarate, IDH1 plays a crucial role in catalysing this reaction. Although, IDH2 performs a similar parallel function to IDH1 but it is located in mitochondria. The diagnosis markers for GBM included microvascular proliferation or necrosis, mutation in TERT promoter and amplification of EGFR gene [13]. HIF-1 (Hypoxia-inducible factor 1) and HIF-2, primarily govern the hypoxic response in GBM. Prolyl Hydroxylases domain (PHD) is responsible for the regulation of HIF-1α. Hypoxia condition inhibits PHD, preventing the degradation of HIF-1α and allowing its accumulation in the cell. HIF-1α govern through the epithelial-to-mesenchymal transition, proliferation, invasion, inflammation, glycolysis and angiogenesis [17-19]. Various genes have found to be upregulated/ downregulated under the influence of hypoxia in GBM. The expression of HIF, IDH1/2, RTK, PI3K, AKT, mTOR, VEGF, MAPK, RhoA/C, EGF, STAT3/bcl2, Wnt/β-catenin, Notch-1, CDK2/6, Snail, MMP-2/9, get upregulated along with reactive oxygen species (ROS) and lipid peroxidation while downregulation of genes like E-Cadherin, Bax, HES1, pCaMK2A, etc have reported in GBM [32-37].

Many therapeutic agents such as curcumin, ellagic acid, bacoside A from *Bacopa monnieri* (BME), some other compounds from ashwagandha, and *Haematococcus pluvialis* target those genes that promote cell proliferation and the growth of cancer cells resulted in the inhibition of tumor growth. These interventions aim to inhibit the expression of genes associated with the aggressive characteristics of GBM, contributing to potential treatment strategies. In the present chapter, we have compiled comprehensive information on the GBM, and its regulation with hypoxia. Also, the use of herbal compounds as therapeutic agents against GBM has also been discussed with recent research data.

2. HYPOXIA SIGNALING AND GBM

The cerebral oxygen levels under normal human physiological conditions are nearly 40 mmHg, in GBM [14]. Hypoxia is characterized by tissue reaching a pO2 value below 10 mmHg, resulting from an imbalance between oxygen supply and consumption to organs [15]. In GBM, hypoxia manifests across a range from mild (pO2 levels from 20 to 4 mmHg) to severe conditions (pO2 levels from 4 to 0.75 mmHg) [15]. The hypoxic conditions in the environment play an important role in determining the prognosis of GBM patients [16,17]. Specifically, the HIF is complicatedly linked to the pathophysiology of GBM, exerting miscellaneous effects on angiogenesis, cell invasion, and

immunosuppression and cell persistence under hypoxia conditions [17-19]. HIF has studied as transcription factor which is responding towards cellular oxygen deficiency. It exists as a heterodimer composed of two subunits which are, HIF-α and HIF-β. HIF-α comprise three isoforms (HIF-1α, HIF-2α, and HIF-3α), HIF-1α is unanimously expressed and tends to be over-expressed in tumor cells and HIF-2α expression is narrowed to specific cell types, such as tumor-associated macrophages (TAMs), while HIF-3α expression is cell-specific, which expresses in the unconfirmed immune cell [20].

Under normal physiological conditions, HIF-1α binds to PHD 1-3 protein which is responsible for oxygen-dependent degradation. It is responsive to oxygen levels as hydroxylates two prolyl residues of HIF-1α through α-ketoglutarate and iron-dependent dioxygenase domains which hydroxylation and facilitates the association with the von Hippel-Lindau (VHL) tumor suppressor protein, that initiate the recruitment of the E3 ubiquitin ligase family and which follows the proteasomal degradation of HIF-1α. [21]. In hypoxia conditions, PHD activity is reduced which leads to the stabilization of HIF-1α protein then it translocate to the nucleus, forming a heterodimeric complex with HIF-1β. The heterodimeric complex binds to hypoxia response elements (HRE) to the promoter or enhancer regions of HIF-1α target genes, this complex occupies in protein-protein interactions with transcription co-activators like cAMP response element-binding protein (CRBP) and p300 [22,23]. It governs the expression of immediate post-hypoxia marker genes, including EPO, GLUT-1, VEGF, Snail, Twist etc.

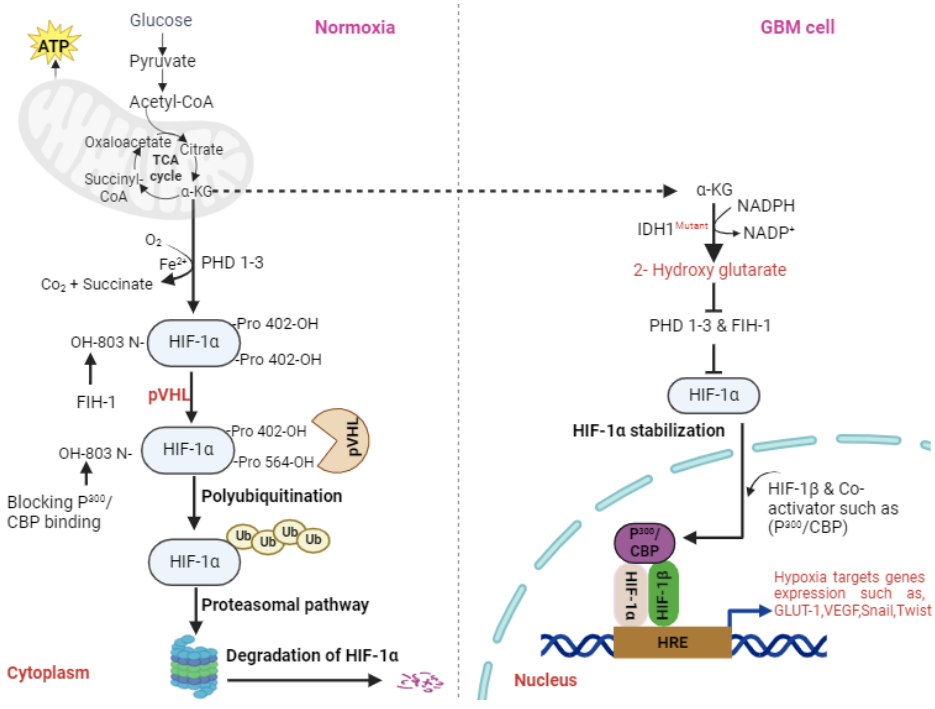


Figure 1: Hypoxia Signaling Pathway in GBM

Hypoxia assumes a central role in GBM [16,17], with HIF-1α being directly linked to GBM pathophysiology. HIF-1α exhibits various effects on cell invasion, cell survival, immunosuppression, and angiogenesis, under hypoxic conditions [17-19]. The presence of HIF-1α has been suggested to the progression of glioma cell from low-grade astrocytoma to GBM. The expressions of mRNA and protein of GLUT-1/3, VEGF, carbonic anhydrase-IX (CA-IX), osteopontin and PDGF-C have correlated with higher pathological tumor grades and poorer diagnoses [24-26]. Furthermore, HIF-1α, VEGF, delta-like canonical Notch ligand-IV (DDL-IV), and PDGF-C are linked to amplified micro-vessel density in both GBM and astrocytomas [27,28]. Hypoxia-related markers, such as CA-IX, and osteopontin, display greater robustness and show powerful correlations with the hypoxia microenvironment and the aggressiveness of GBM compared to HIF-1α. Studies reveal that in GBM tissue HIF-1α in areas surrounding necrosis, predominantly in the nuclei, whereas in low-grade gliomas, HIF-1α found and primarily expressed and localizes in the cytosol [29,30]. Regulatory mechanisms that control HIF-1α in the tumor includes the activation of oncogenes like EGFR or the loss of tumor suppressors like p53 or PTEN [31].

Studies have demonstrated alterations in various signaling pathways in GBM including HIF/IDH1/2, VEGF, AKT/PI3K/RhoAC/mTOR, EGF, MAPK, STAT3/bcl2, Notch and Wnt/β-catenin [32-37]. Research suggests that ING-5, a member of the epigenetic regulator's ING family, may augment PI3K/AKT activity by facilitating the transcription of the Ca^{2+} channel and follicle-stimulating hormone signaling genes. Hypoxia induces the upregulation of Delta-like non-canonical Notch ligand-1 (DLK-1) which promotes colony formation and gene expression of GSC (GBM stem cell) markers [38]. A recent study demonstrated that CBF-1 is activated by hypoxia and it is found to be a key transcriptional modulator in the Notch signaling pathway, promoting GSC proliferation and accelerating epithelial-to-mesenchyme transition (EMT), thus increasing chemo-resistance in GBM [39].

Vascular endothelial growth factor (VEGF) is a pro-angiogenic factor that influences angioedema and vascular permeability with VEGFR-2 acting as its receptor. In hypoxic conditions, VEGF and VEGFR2 are both up-regulated by HIF1α, resulting in overexpression in glioblastoma and subsequently accelerating tumor advancement and invasion [40]. Further, HIF-1α expression can lead to activation of the JAK-STAT pathway which closely linked to VEGF secretion, thereby promoting the self-renewal of GSCs [41]. Anti-VEGF monoclonal antibody, is utilized as a second-line agent demonstrating effectiveness in reducing peculiar vascularization in GBM [42, 43]. Investigation suggests that potential targets of both anti-VEGF and

immunologic effects resistance are facilitated by the elevation of regulatory T-cells in GBM [44].

The Wnt pathway is intrinsically associated with GSC, capable of reducing CD133 and nestin under anaerobic and aerobic conditions. In hypoxic environments, HIF-1α upregulates LEF-1 and TCF-1 expression which is associated with Wnt signaling in GBM. This associated reprograms the GSC phenotype towards a more differentiated and less aggressive state. Many studies show that hypoxia-induced Wnt activation inhibits the Notch pathway in primary GBM, enhancing the chemo-sensitivity towards temozolomide therapy [45]. Hypoxia signaling pathway implicated in normoxia and GBM is clearly depicted as figure 1.

Transforming growth factor (TGF), with its two isoforms TGFβ1/β2, functions as a downstream gene of HIF-1α and plays central role in the progression and recurrence of glioblastoma [46]. TGFβ is identified as an upstream regulator and co-modulator of VEGF, and it signaling pathways could effectively manage the neoplastic growth of GBMs [49]. The *in vitro* study has shown the implication of TGFβ in promoting the invasion of GSCs [47]. Overexpression of integrin αvβ8 in GSCs is pivotal for self-renewal, tumorigenesis, and its progression is facilitating TGF-β1 which induces DNA replication, suggesting that the αvβ8-integrin TGF-β1 axis could serve as a therapeutic target for glioblastoma [48]. In GBM, dedifferentiation of non-stem cells into stem cells is associated with EMT, resulting in an increased quantity of GSCs and poorer outcomes for GBM patients [46].

Many studies have shown that natural herbs as curcumin, BME, ellagic acid, ashwagandha, and *H. pluvialis* have anti-glioblastoma potential in either alone or in combination with other chemotherapies. These natural herbs represent anti-tumor activity by repressing the cell cycle which inhibits the progression of cancer including GBM. Several plant products such as bacoside A, alkaloids, flavonoids, astaxanthin and adonixanthin have been utilized in the context of their influence by arresting the cell cycle progression. Evidences also strengthened that a variety of plant derived sources favors to downregulate aberrant biological pathways.

3. POTENTIAL ROLE OF HERBAL COMPOUNDS IN THE PREVENTION OF GBMTOP OF FORM

1. Curcumin

Curcumin, derived from *Curcuma longa* L, has garnered significant attention due to its diverse array of therapeutic properties, including antioxidant,

antiproliferative, immunomodulating, radioprotective, chemopreventive, antitumor, anticarcinogenic, and anti-inflammatory actions [52-63]. The major active components of turmeric are curcuminoids, which are composed of curcumin, desmethoxycurcumin, and bisdemethoxycurcumin in the ratio 77:17:3. Among these curcumin is the main compound and is a potential therapeutic agent against different chronic diseases such as cardiovascular, neurodegenerative and pulmonary diseases, along with various other autoimmune conditions [64, 65].

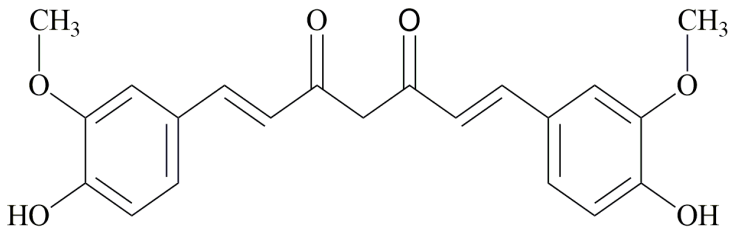


Figure 2: The Molecular Structure of Curcumin

Curcumin has demonstrated the ability to restore DNA methyltransferase (DNMT) functions and oxidative stress in the context of diabetic retinopathy [63]. Additionally, curcumin has been identified as a promoter of wound healing by facilitating fibroblast migration and collagen synthesis [66]. The anticancer effects of curcumin have demonstrated against various cancers including GBM via targeting tumor growth, migration, invasion, cell death, and proliferation [67-75]. The common targets affected by the curcumin are p53, P13K/AKT, JAK-STAT, NF-κB, retinoblastoma (Rb), MAPK and sonic hedgehog [76-82]. A possible mechanism through which curcumin inhibits autophagy, increases cell death and arrest the cell cycle progression is depicted in figure 3.

Due to the lipophilic nature of curcumin, it can pass the blood–brain barrier (BBB) [83,84], it can be a potential therapeutic impact on GBM. The selectivity of curcumin is only towards tumor cells since the inhibition of the P13K/AKT signaling by curcumin induces G2/M phase arrest as an early phase in the apoptotic mechanism. Curcumin has involved in reduction of tumor size while increment in apoptotic cells [85]. The increase in apoptosis of cancer cells by curcumin is due to the upregulation of PTEN by curcumin followed by the downregulation of p-mTOR and p-AKT expression which finally leads to apoptosis of cancer cells. Curcumin induces autophagy through the inhibition of pathways such as AKT, mTOR, and p70S6K [86,87]. Curcumin increases the BAX/BAD which leads to the release of cytochrome-c followed by activation of caspase-3 and downregulation of Bcl2 [88]. Curcumin in combination with nimustine hydrochloride inhibits the phosphorylation of P13K/AKT [89-91].

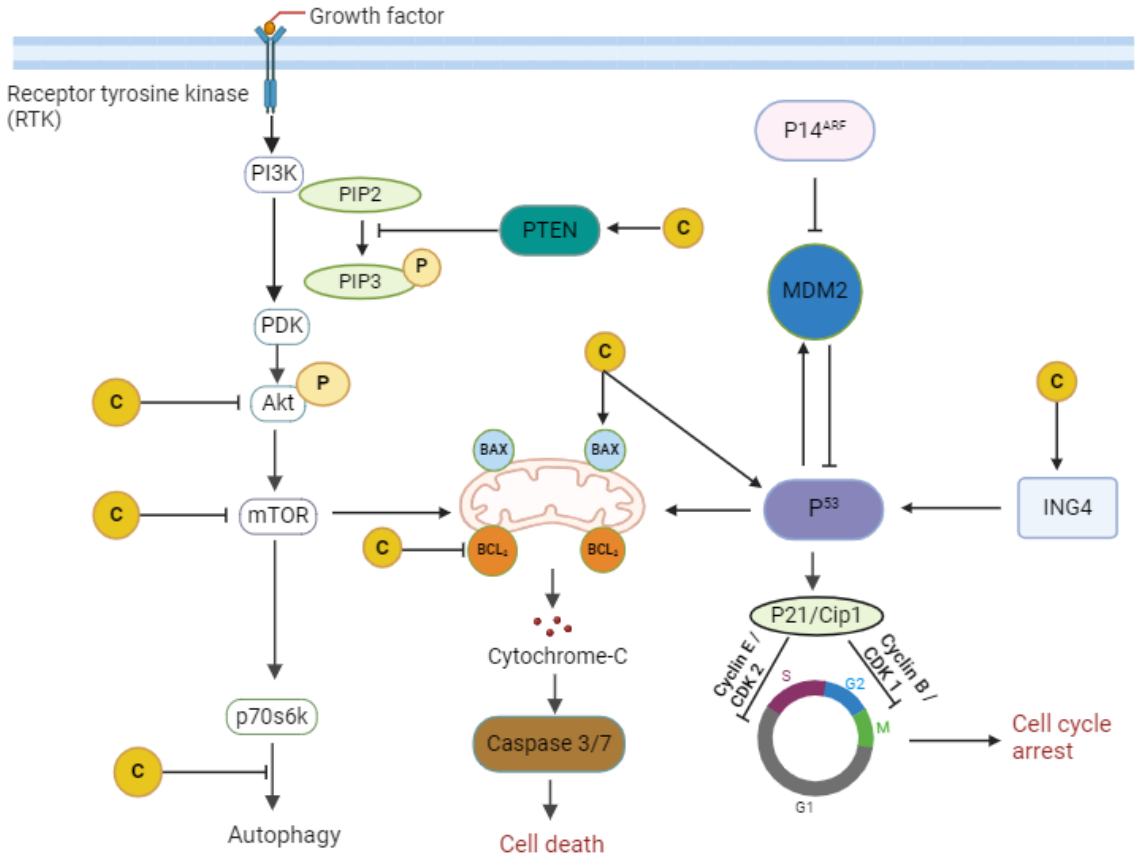


Figure 3: Curcumin exhibits its anti-cancer effects in GBM by impeding key molecular targets through the inhibition of signaling pathways and their subsequent downstream components. such as PI3K/AKT and p^{53} pathway with upregulation denoted by → and downregulation indicated by ⊣ .

2. Ellagic Acid

Ellagic acid, a naturally polyphenol found in various plants like as grapes, pomegranates, nuts, etc has attracted much of attention for its diverse health benefits. Studies have revealed its antioxidant, anti-allergic, anti-inflammatory, and ischemia-reperfusion injury properties, along with notable anti-tumor effects [112]. In different malignant tumor like breast, lung, liver cancer, nasopharyngeal carcinoma, myeloma, and prostate cancer ellagic acid shows anti-tumor effects by inhibiting cell proliferation, promoting apoptosis pathway, restraining invasion and metastasis through different molecular mechanisms [113]. Ellagic acid shows inhibitory effect on tumor growth by a downregulating in AKT/Notch signaling in GBM. Additionally, ellagic acid upregulated the expression of E-cadherin while blocking the expression of cyclin D1, CDK2/6, Bcl-2, MMP-2/9, and snail [114]. Implication of ellagic acid in GBM is shown as figure 4.

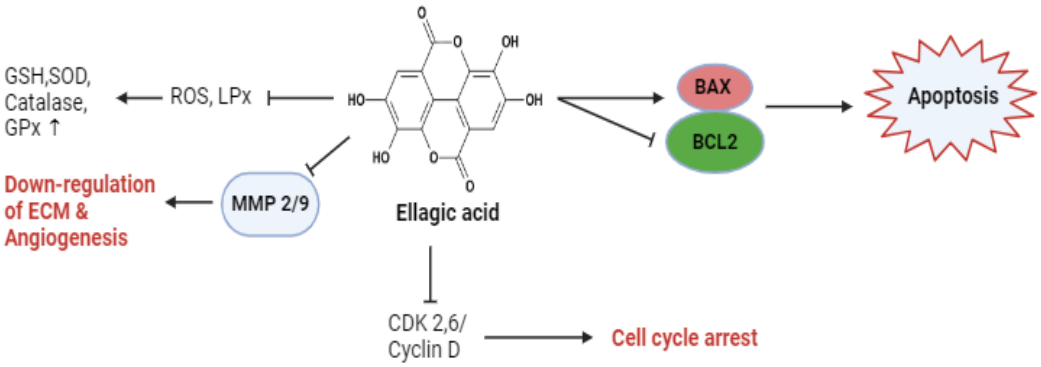


Figure 4: Ellagic Acid Exhibits its Anti-Cancer Effects in GBM

3. Bacopa Monnier

Bacopa monnieri generally known as 'Brahmi,' is an important therapeutic plant well-known as Indian traditional ayurvedic medicine. Belonging to the scrophulariaceae family, this small perennial herbaceous plant has been utilized in ayurvedic medicine practices for over three thousand years, particularly as a memory enhancer [92,93]. It is known for its roles in the treatment of various nervous disorders, digestion problems, anxiety, and also enhance learning, memory, and concentration. It is also used as neuroprotector, anticancer, antidiabetic, antipyretic, antilipidemic, adaptogenic, antiepileptic, gastrointestinal, cardiovascular, smooth muscle relaxant, analgesic, antihypertensive, antimicrobial, and anti-inflammatory. Particular uses include addressing conditions such as asthma, insanity, and epilepsy [94-99]. Bacopa herb is involved in the repair of damaged neurons as well as the synthesis of neurons, restoration of synaptic plasticity activity, and overall protection of CNS function. *B. monnieri* contains various metabolites such as alkaloids (brahmine), bacosides, saponins, triterpenoids, saponins, stigmastanol, β-sitosterol, α-alanine, serine, D-mannitol, betulinic acid, aspartic acid, glutamic acid, stigmasterol, nicotinine, and herpestine [100]. Notably, Bacoside A has been found to induce dose-dependent apoptosis in GBM. It concurrently reduces Notch1 expression while increasing the levels of HES1 expression [101]. The precise mechanism underlying Notch1 downregulation and HES1 upregulation in the presence of Bacoside A warrants further investigation. Bacoside A has potential anti-cancer activity against GBM cells [102-111]. Implication of bacoside-A, A3, bacopaside-II, and saponin-C in the modulation of GBM is shown in figure 5.

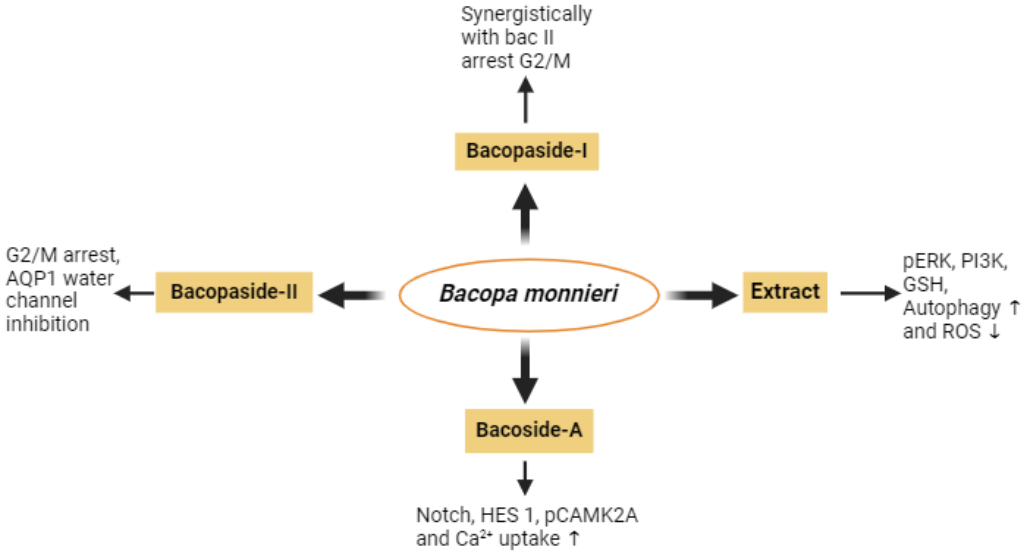


Figure 5: Major targets of active constituents from *Bacopa monnieri* for anti-cancer activity. Upregulation (↑) & and downregulation (↓) denoted by the arrow.

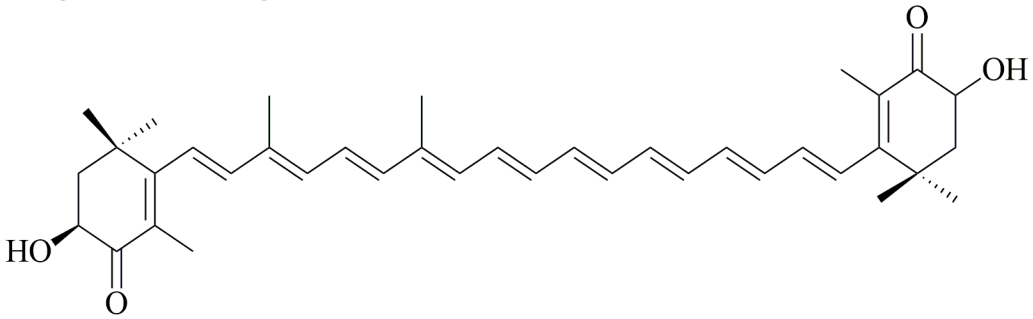
4. Ashwagandha

Ashwagandha, systematically known as Withania somnifera belonging to the solanaceae family, is commonly known as "Indian ginseng" or "Winter cherry." The plant's various parts, including berries, flowers, leaves, stem, and roots, contain major bioactive phytochemicals such as steroidal lactones (withanolides), alkaloids, flavonoids, saponins, tannins, terpenoids, and their derivatives. Withanolides like withanolides A to Y, withasomniferols A to C, dehydroxy withanolide R, withasomniferol A, withasomnine, withaferin-A, & withanone, along with alkaloids such, somniferine, anahydrine, somnine, somniferinine, withananine, psuedowithanine, tropine, cuscohygrine, isopelletierine, anaferine, cuscohygrine, tropine, withanine, pseudotropine, and ashwagandhine have been identified. additionally, several sitoindosides have been isolated [115-120]. The antitumor effect of withaferin A (WA) in GBM which is the most common malignant brain tumor, has been explored due to the limited success of existing treatments. Despite the poor prognosis associated with GBM, WA offers a potential novel approach to treatment. While the specific mechanism of WA antitumor action in GBM remains unclear, it has been observed to modulate multiple oncogenic pathways simultaneously. Interactions with proteins like as AKT/mTOR/MAPK and NF-κB have been identified as part of WA's anti-proliferative activities. WA induces cell cycle arrest by blocking CDK and cyclin, and apoptosis in tumor cells, and modulates HSP70/HSP90 protein chaperones in GBM. Moreover, it demonstrates a cooperative effect with temozolomide (TMZ) and radiotherapy. Recent studies on WA and GBM stem cells further support their anti-tumor actions. Despite

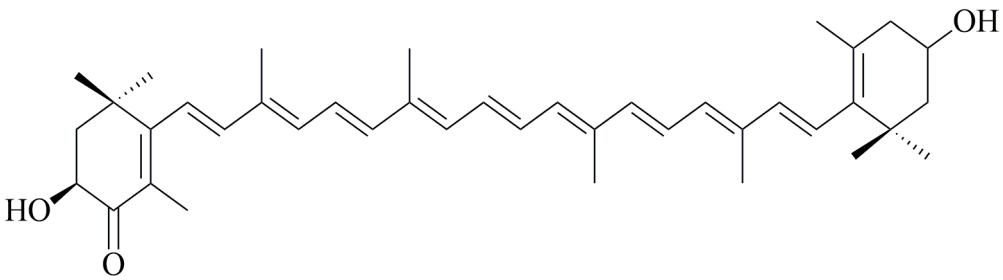
promising preclinical findings, human trials of WA on GBM are yet to be undertaken [32-34,36].

5. Haematococcus Pluvialis

Astaxanthin is a xanthophyll carotenoid, primarily sourced from *H. pluvialis* [121,122]. As a red lipid-soluble pigment, astaxanthin is known for its potent antioxidant, antidiabetic, anticancer, neuroprotective properties, antimicrobial properties, anti-inflammatory effect, immune-stimulatory or modulatory, and cardioprotective [123]. Adonixanthin shows similar properties with astaxanthin i.e. possessing strong antioxidative effects. Both astaxanthin and adonixanthin has bears antitumor properties and therapeutic effects on the CNS [124-128]. Astaxanthin has previously shown antitumor effects against various cancers, including bladder carcinogenesis, hepatocellular carcinoma, colon carcinogenesis, oral cancer and leukemia [129-134]. However, the precise mechanisms underlying astaxanthin's antitumor activity are still not fully elucidated. Existing literature suggests that the antitumor effects of astaxanthin and adonixanthin involve multiple types of mechanisms, such as ERK, NF-κB, PPARγ, AKT (PKB), JAK-2/STAT-3, and Nrf2 [135]. It is supposed that astaxanthin and adonixanthin possess antitumor effects against glioblastoma by inhibiting the phosphorylation of Akt and ERK1/2 while upregulating the expression of phosphorylated p38, which leads to cell apoptosis and cell cycle arrest [136,137]. These findings underscore the potential of astaxanthin in combating GBM through multifaceted molecular mechanisms.



Astaxanthin



Adonixanthin

Figure 6: Molecular Structure of Astaxanthin and Adonixanthin

Table 1: Plant Source, Protein/Pathway Involved and Mechanism of Natural Compounds

Class	Chemical Compound	Source	Protein/Path-way Involved	Mechanism Effect	Reference
Flavonoids	Quercetin	Apples, broccoli, red grapes, red onions, berries and cherrie	IL-6, STAT3	Cell Proliferation ↓	141
	Icariin	*Herba epimedii*	NF-κB	Apoptosis ↑ and cell proliferation ↓	142
	Jaceosidin	*Artemisia argyi*	Bax, p53, caspase-3	Cell cycle ↓ and apoptosis↑	143
	Rutin	*Dimorphandra mollis*	VEGF, TGF-β1	Cell migration, invasion and angiogenesis ↓	144
	Procyanidins	Cinnamon, apples, grape skin	HIF-1α, MMP-2, VEGF, GPCR	Invasion and angiogenesis ↓	145, 146
	Deoxypodophyllotoxin	*Dysosma versipellis*	Cdc2, Bcl-xL, Bcl-2, Cyclin	Cell cycle ↓, apoptosis ↑	147
	Silibinin	Seeds of milk thistle	STAT3, miR-7-1-3p	Apoptosis ↑	148-150
Polyphenol	Resveratrol	Peanuts, mulberries and grapes	MGMT, XIAP, Bcl-2, AMPK, NF-κB	cell cycle ↓; TMZ resistance ↓	151, 152
Diterpenoid lactone	Andrographolide	*Andrographis paniculata*	CDK1, CDc25C, PI3K/ AKT/mTOR	Cell cycle ↓; cell proliferation ↓	153
Terpenoid	Oridonin	*Rabdosia rubescens*	RanGAP1 and RanGTP	Apoptosis ↑	154
Triterpene saponins	Betulinic acid	*Prunella vulgaris, Betula pubescens*	p53, caspase-PARP cascade, BetA	Apoptosis ↑	155, 156

	Ginsenoside Rg3	Panax ginseng	VEGF-A, Bcl2	Cell cycle, proliferation and angiogenesis ↓	157
Xanthone	γ-Mangostin	*Garcinia mangostana*	ROS	Apoptosis ↑	158
Alkaloid	Berberine	*Berberis aristate, Berberis aquifolium, Tinospora cordifolia*	EGFR-RAF-MEK-ERK signaling	Apoptosis ↑	159
Lectins	Mistletoe lectins	*Viscum album*	TGFBR2, MMP, TGF-β,	Modulate gene expression	160
Plant protein	Trichosanthin	*Trichosanthes kirilowii*	Wnt/β-catenin LGR5,	Cell proliferation ↓	161

4. CONCLUSION

GBM is the most destructive brain tumor responsible for the approximately 16000 deaths per year. Pathophysiology of GBM, exhibiting a wide range of effects on various aspects such as cell invasion, angiogenesis, immunosuppression, and cell survival. The intricate relationship between HIF-1 and GBM underscores its significance in influencing key processes associated with the development and progression of this aggressive brain tumor. Treatment for this cancer is either surgical removal or radiation therapy but both of these methods are risky and have many side effects on the body. Apart from these treatment methods the phytotherapy is emerging as the additional method to increase the efficiency of cancer treatment. Many Indian traditional herbs have the potential therapeutic properties against various types of tumor including GBM. Herbs like ashwagandha, brahmi, chemicals like curcumin, ellagic acid are involved in the inhibition of brain tumor growth. These herbs possess many unique metabolites which interact with the signaling molecules. So the existing chemotherapy could be combined with the plant-derived source for better treatment and diagnoses against GBM. Further studies are needed to elucidate the molecular mechanism involved in the phytochemicals and tumor's cell response.

Conflict of Interest: Authors have no Conflict of Interest.

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