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REVIEW ARTICLE

Polyphenols Modulate the miRNAs Expression that Involved in Glioblastoma

Maede Rezaie[1], Mohammad Nasehi[2], Mohammad Shimia[3], Mohamad Ebrahimnezhad[1], Bahman Yousefi [1,5,*] and Maryam Majidinia [4,*]

[1]*Department of Clinical Biochemistry and Laboratory Medicine, Faculty of Medicine, Tabriz University of Medical Science, Tabriz, Iran;* [2]*Cognitive and Neuroscience Research Center, Amir-Almomenin Hospital, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran;* [3]*Department of Neurosurgery, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran;* [4]*Solid Tumor Research Center, Cellular and Molecular Medicine Institute, Urmia University of Medical Sciences, Urmia, Iran;* [5]*Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

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Abstract: Glioblastoma multiforme (GBM), a solid tumor that develops from astrocytes, is one of the most aggressive types of brain cancer. While there have been improvements in the efficacy of treating GBM, many problems remain, especially with traditional therapy methods. Therefore, recent studies have extensively focused on developing novel therapeutic agents for combating glioblastoma. Natural polyphenols have been studied for their potential as chemopreventive and chemotherapeutic agents due to their wide range of positive qualities, including antioxidant, anti-inflammatory, cytotoxic, antineoplastic, and immunomodulatory activities. These natural compounds have been suggested to act *via* modulated various macromolecules within cells, including microRNAs (miRNAs), which play a crucial role in the molecular milieu. In this article, we focus on how polyphenols may inhibit tumor growth by influencing the expression of key miRNAs that regulate oncogenes and tumor suppressor genes.

Keywords: Glioblastoma, glioma, miRNAs, non-coding RNA, polyphenols.

1. INTRODUCTION

Cancer is a disease in which cells throughout the body grow and divide abnormally and then spread to other organs and parts of the body [1]. Neurons and glial cells together form the human brain. Malignancy may develop in the brain when glial and neuronal cells proliferate and expand at an abnormally high rate. A key factor in the development of the diseases is the molecular microenvironment. In the United States, there are 3.19 new instances of glioblastoma multiforme (GBM), a solid tumor that develops from astrocytes, for every 100,000 people. Brain tumors like GBM tend to spread quickly and be lethal. However, despite the fact that standard medical and surgical therapies have increased survival rates, difficulties still exist, including tumor heterogeneity, invasiveness, and chemotherapeutic resistance [2]. GBM rates vary greatly amongst demographic subsets, with men and the elderly being especially susceptible to the illness. GBM has a dismal prognosis, with a median survival rate of less than a year [3]. The GBM subtype is the most severe and aggressive brain tumor of all cancer types, and it is partially incurable despite standard treatments such as radiation therapy in combination with chemotherapy and surgical removal of the tumor, followed by radiation therapy [4]. While there have been improvements in the efficacy of treating GBM, many problems remain, especially with traditional therapy methods. The significant penetration of GBM and its ill-defined limits, for example, might make it difficult to remove the tumor surgically and decrease survival rates [5]. Chemotherapeutic medications risk losing some of their efficacy if patients develop resistance to them [6].

MicroRNAs (miRNAs) play a crucial role in the molecular milieu. Post-transcriptional regulation of gene expression by short, non-coding RNAs. When compared to other tissues, the number of miRNAs expressed in the brain is very high. In contrast to the continuous decrease in miRNA expression seen in oncogenic progression, increased miRNA expression is seen in the first stages of neurodegeneration. It is hypothesized that the emergence of brain cancer is due to dysregulation in the miRNAs' control of cell proliferation, differentiation, and death [7]. Phenolic compounds have antioxidant properties and also possess antiviral, anticarcinogenic, anticancer, and antibacterial [8]. Natural polyphenols have been studied for their potential chemopreventive and chemotherapeutic potential due to their wide range of positive qualities, including antioxidant, anti-inflammatory, cytotoxic, antineoplastic, and immunomodulatory activities [9, 10]. To better understand the molecular anticancer processes at work in natural polyphenols, this study will examine the

*Address correspondence to this author at the Solid Tumor Research Center, Cellular and Molecular Medicine Institute, Urmia University of Medical Sciences, Urmia, Iran; E-mail: majidinia.m@umsu.ac.ir

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current evidence for their use as adjunctive drugs and to improve the efficacy of chemotherapy. Among the many bioactive compounds studied for their potential in cancer prevention and treatment, resveratrol, curcumin, quercetin, epigallocatechin-3-gallate and coumarin derivatives have shown dose-dependent improvement in effectiveness [11]. Polyphenols may alter transcription factors and miRNAs as well as interact with cell signaling pathways and influence gene expression. Cannabinoids, terpenes, and curcumin have the most data supporting or implying their therapeutic utility in slowing the progression of GBM *via* mechanisms such as chemosensitization or reduced migration and cell invasion. Therefore, natural chemicals may provide hope for the development of medicines to combat GBM progression [12]. In this article, we focus on how polyphenols may inhibit tumor growth by influencing the expression of key miRNAs that regulate oncogenes and tumor suppressor genes.

2. GLIOMA AND GLIOBLASTOMA

Brain Tumor Initiating Cells (BTICs) are the cause of brain cancer and may result in the growth of a fully heterogeneous malignancy [13]. Based on unique markers and stem cell-like characteristics, these cells may be distinguished from other cells. There are many different forms of brain cancer, with GBM being the most harmful. Only 3.3% and 1.2%, respectively, of GBM patients survive after two and three years [14]. This illness is very fatal and has a negligible response to treatment or radiation. It is difficult to identify and treat this terrible illness since GBM exhibits vast variability in cellular and genetic makeup, even at the level of a single cell [15]. Gliomas are malignancies that develop from the brain's supporting cells, and they account for around 80% of malignant brain tumors and 30% of all central nervous system tumors [16, 17]. The World Health Organization divides gliomas into four subtypes: oligodendroglioma, astrocytoma, ependymoma, and pilocytic astrocytoma [18]. Histopathological characteristics, such as nuclear polymorphism, increased mitotic activity and cellularity, neovascularization, and necrosis, form an additional grading system for tumor categorization (I-IV) [19]. Primary malignant brain neoplasm glioblastoma accounts for 16% of all primary brain and central nervous system (CNS) cancers. The incidence rate is 3.2% per 100,000 people per year. GBM occurs in different parts of the brain, including the brainstem, cerebellum, and spinal cord [20, 21]. It was previously thought that glial cells were the only possible source for GBM. However, new research suggests that they may originate from other cell types that have brain stem cell properties, from stem cells to neurons to glial cells. Changes in signaling pathways at the molecular level are made. These cells go through many distinct phases of development [22].

Most primary and secondary GBM have alterations in these signaling pathways, which cause uncontrolled cell proliferation and increase cell viability, help tumor cells pass through cell cycle checkpoints and avoid cell apoptosis [23]. Primary and secondary gliomas have similar molecular alterations and gene expression patterns. Overexpression of the epidermal growth factor receptor (EGFR), mutations in phosphatase and tensin homologue (PTEN), and deletion of chromosome 10q are defining genetic alterations in primary GBM. However, p53 mutations, isocitrate dehydrogenase 1 (IDH1) mutations, and the deletion of chromosome 19q are highly correlated with secondary GBM. Significant implications for the development and therapy of GBM arise from these genetic changes [24]. On the other hand, in GBM, neural and mesenchymal cells have all been identified as separate subtypes with their own disease progression rates and survival rates. Drug efflux, DNA damage repair, and miRNAs are just a few of the main mechanisms of drug resistance that we have addressed in this study. Many other plant-derived medicines and alternative and adjunctive medicines have been studied as primary or possible adjunctive therapies to address these processes [25].

The average survival rate of glioblastoma patients has not increased much compared to the last decade. Patients with glioblastoma who receive treatment (surgery, radiation and chemotherapy) have a 9.8% chance of 5-year survival. Drug resistance is one of the effective factors in reducing the survival rate of these patients [26]. There are two main types of drug resistance to consider: acquired and inherent. When a tumor that has been receptive to treatment suddenly stops responding to the anticancer therapy, this phenomenon is known as acquired resistance. However, when the tumor shows little to no response to the therapy at the outset of treatment, this is known as intrinsic resistance. Recent research has shown, however, that there are many molecular similarities between the two kinds of resistance [27]. Important treatment targets for restoring sensitivity to apoptosis may be identified by studying the molecular connection between GBM cells and their environment since these anomalies might be an indicator of tumor growth and progression. Consequently, one of the primary objectives in the management of glioblastomas is the delineation of the cellular and molecular processes that impart drug resistance [26].

3. MiRNA

The genome encodes critical regulatory elements called miRNAs. They can effectively turn off a number of genes involved in various processes. Given the many genetic alterations that define cancer, emerging techniques that focus on discovering and modifying miRNA pathways hold promise for advancing cancer therapy. Up-to-date understanding of miRNA biogenesis, miRNA role in cancer resistance, and tools needed to modulate miRNA expression [28]. Pathophysiology, tumor plasticity, and therapeutic resistance in GBM all depended on miRNAs. Glioma subtypes and even subpopulations of the same tumor express miRNAs differently in the tumor mass compared to normal brain tissue [29]. MiRNA expression variations have the potential to be used as diagnostic and prognostic biomarkers. The capacity of a single miRNA to target several genes involved in distinct biological activities is what gives miRNAs their major therapeutic benefit [30].

4. MicroRNA: STRUCTURE, BIOLOGY AND SYNTHESIS

RNA polymerase II or III is the enzyme that first synthesizes miRNA in the nucleus, producing enormous pri-miRNA transcripts. After that, the cytoplasm and nucleus

undergo processing to produce mature miRNAs from these immature miRNAs. A microprocessor complex made up of the double-stranded RNA binding protein DGCR8 (sometimes referred to as pasha) and the riboendonuclease enzyme Drosha, a member of the RNase III family, initiates the maturation process in the nucleus. Drosha is a double-standard RNase III enzyme that cleaves double-standard RNA at the pri-miRNA stem-loop. It is composed of two domains. According to reports, Pasha is the only source of drosha's action. In *Drosophila* and *Caenorhabditis elegans*, the lack of pasha causes immature miRNA to accumulate in the cytoplasm [31]. This "microprocessor complex" creates lengthy precursor miRNA, which has a hairpin-like form and is around 70 nucleotides long. It also converts primary miRNA, or pri-miRNA, into precursor miRNA, or pre-miRNA. Furthermore, it cleaves by RNase-III, producing a distinct 2-nucleotide overhang at the 3' end [32]. Dicer, a processing enzyme, and exportin-5 have specifically discovered this characteristic. Pre-miRNA is moved from the nuclear envelope into the cytoplasm *via* a process that depends on exportin 5 and ranGTP [33]. The majority of nuclear macromolecules (40 kD) in eukaryotes are transported *via* importins (for entrance) and exportins (for exit). From the nucleus to the cytoplasm, exportin-5 transports primiRNA in a carrier molecule-like manner. Notably, exportin-5 also has a RanGTP receptor binding site. The main nuclear protein is called Ran, and it may be found in the cytoplasm as GDP and the nucleus as GTP and GTP, respectively. The hydrolysis of RanGTP into RanGDP during transport facilitates the release of pri-miRNA into the cytoplasm from the microprocessor complex. The RNase III enzyme DICER1 processes pri-miRNA in the cytoplasm. With the help of its two catalytic domains, DICER1 attaches itself to pri-miRNA. It then cleaves in the direction of the stem-loop end to produce mature duplex pre-miRNA, which is about 22 nucleotides long. An RNA-binding protein called transactivation-responsive RNA-binding protein (TRBP) improves the cleavage of a subset of miRNAs that DICER1 mediates. The mature miRNA duplex subsequently forms the miRNA-induced silencing complex (miRISC) by binding to the argonaute (Ago 1-4) protein. One of the main proteins in the RISC complex, Ago 2, is involved in translation suppression or mRNA degradation. However, the miRNA attaches to the 3' end of the untranslated region (UTR) and supplies a complementary base to the target mRNA. MiRNAs identify their target mRNA by a unique sequence known as the seed region (5' end miRNA; 2-7 nucleotides). Significantly, a single miRNA may target several mRNAs due to the small seed region. mRNA degradation may result from a high level of complementarity between the seed region and the target mRNA. The target mRNA experiences translation inhibition when the complementarity is poor. Nonetheless, mRNA translation may be prevented by any method. Ultimately, the mature miRNA directs the RISC complex to the appropriate target mRNA in order to suppress translation or degrade it [34].

5. ROLE OF miRNAs IN CANCER

Human brain development and related illnesses include several miRNA regulation mechanisms. Cell-to-cell variation in miRNA expression strongly supports the notion that miRNAs are expressed on a case-by-case basis and that their expression is thus cell-specific [35]. When used in the study of neurological pathology, miRNA profiling reveals surprising insights into processes, including neurodegeneration and oncogenesis. When compared to other organs, the brain has a high concentration of miRNAs [15]. This lends credence to the idea that they control a wide variety of pathological and physiological brain processes. Because of their ability to target numerous mRNAs, a single miRNA may influence the expression patterns of several mRNAs, allowing for broad manipulation of genes. Profiling the microRNAome helps them perform their unique roles in different cells and tissues. Neurodegenerative diseases and brain tumors both provide evidence of altered expression levels of miRNAs. The only part of the brain where miR-124 is not strongly expressed is the pituitary. Neurodegeneration, brain cancer, synapse architecture, chronic stress, and neurodevelopment have all been linked to this miRNA [36]. Hundreds of non-neuronal genes are repressed by miR-124 in neurons, assisting in the development of neuronal identity; conversely, the inactivation of miR-124 results in the expression of non-neuronal genes [37]. Multiple degenerative diseases of the central nervous system are brought on by an imbalance of miR-124. MiR-124 expression was downregulated in malignant brain tumors. When miR-124 is reintroduced into glioblastoma cells, the tumor cells undergo morphological alterations, including a decrease in proliferation, motility, and invasion [38]. The available data suggest that miR-124 modification might be a useful therapeutic target for treating neurological disorders like brain tumors. During typical brain development, miR-128 is involved in neurogenesis and synaptogenesis [39]. miR-128 directs neural progenitor cells toward neural differentiation. The expression of this microRNA exists in all kinds of brain diseases [40]. Downregulation of miR-128 is seen in malignant glioma and brain medulloblastoma, on the other hand. Neurodegenerative diseases are also associated with deregulation of miR-128 [41]. Many studies on the involvement of miRNAs in the development of cancer have been published in the last few decades. More than 24,000 peer-reviewed scholarly publications have been published on this subject since its discovery. Remarkably, a large number of miRNA genes are situated in genomic areas that are known to be connected to cancer and are impacted as the illness progresses [42]. Numerous cancer tissues have shown that a number of miRNAs are involved in the carcinogenesis process. It is noteworthy that several kinds of miRNAs have been shown to be present in various tumor types. Furthermore, while comparing tumor samples to their corresponding normal tissues, it was discovered that there were significant changes in the expression pattern and biogenesis route of miRNAs [43]. MiRNA gene loss, translocation, and amplification have often been seen in cultivated cancer cell lines and advanced cancer tissues [44]. For instance, the first human miRNAs linked to cancer were found in miR-15/16 clusters. In cases of CLL or chronic lymphocytic leukemia, these clusters are often eliminated. In general, the antiapoptotic protein BCL-2 is regulated by miR-15/16 clusters. Aberrant expression of BCL-2 is seen with suppression of the miR-15/16 clusters. Furthermore, BCL-2, an oncoprotein, aids cancer cells in evading apoptosis, a well-known feature of human cancer [45]. Researchers have recently placed a great deal of emphasis on

finding tissue-specific miRNA for therapeutic applications and cancer diagnostics. It's noteworthy that Ferracin and associates [46]. Even in the absence of sample characteristics, the miRNA profiles have been used to pinpoint the cause of cancer. Examining the expression of signature miRNA may help identify certain forms of human cancer and enhance cancer treatment. Single nucleotide polymorphisms (SNPs) have been connected to aberrant miRNA expression. SNPs can alter miRNA expression and influence the onset or course of cancer [47]. Furthermore, SNPs prevent the target mRNA from degrading in seed areas. For example, if let-7 miRNA has an SNP, it will no longer complement the 3' UTR in KRAS mRNA, which might result in the development of non-small cell lung cancer [48]. Moreover, the development of renal carcinoma, colon, breast, and chronic lymphocytic leukemia (CLL) is influenced by SNPs in miRNA. SNPs have been shown in these investigations to have a major role in miRNA function. The occurrence of SNPs is linked to the development of different kinds of cancer [49].

6. ROLE OF microRNAs IN GLIOMA

Studies on dysregulated miRNA and their function in the development of gliomas have shown their importance in key signaling pathways. These pathways are crucial in identifying glioma features that affect prognosis and response to therapy. They also provide possible targets for biomarker development. We may find certain miRNA biomarkers for uses, such as diagnosis or therapy selection, by comprehending how miRNA affects signaling pathways and progression. An outline of the function of miRNA in these pathways, which impact glioma behavior and support a number of traits, including invasion, migration, and proliferation, is given in this section. Considering that the first miRNA was discovered in 1993, this area has advanced significantly. MiRNA's maturation and biosynthesis have been well studied [50]. The basic process of miRNA biogenesis is the creation of a primary miRNA as a consequence of the transcription of the miRNA gene (pri-miRNA). The pri-miRNA is processed to produce a stem-loop precursor miRNA (pre-miRNA). After the pre-miRNA is cleaved, a miRNA duplex is formed, which is then separated into mature 5p and 3p miRNA strands. The orientation of the seed sequence determines the names of these strands. The mature miRNA strand that has been cut free from the RISC complex is referred to as miRNA. Recent studies have shown new levels of complexity in miRNA control, suggesting that dysregulation of maturation and biosynthesis may aid in the development of cancer. Furthermore, it has been shown that RNA editing regulates the synthesis of miRNA. A to I editing is the process by which adenosine in prim-miRNA transcripts is changed from adenosine to inosine by adenosine deaminase acting on RNA (ADAR) [51]. It has been shown that adenosine-to-inosine (A-to-I) editing affects the processing of pri-miRNA. Numerous investigations have shown that this editing process may result in a reduction in mature miRNA levels [52]. Moreover, mature miRNA molecules with modified sequences known as "isomiRs" can also be produced by A-to-I editing. These isomiRs may play a role in the development of tumors and may target many mRNA transcripts. Evidence shows that malfunctioning ADARs cause A-to-I editing in gliomas, especially high-grade gliomas [53]. Alterations made to the seed sequence can change a miRNA's target, upsetting the control over protein production and accelerating the course of illness [53]. On the other hand, modifications in gene and protein expression may also result *via* non-editing. For example, research found that lower expression of ADAR and its isoform ADARB1 in glioblastoma resulted in reduced editing of the miR-376 cluster. Unedited miR-376a-3p transcripts accumulated as a consequence, and it was shown that these enhanced the glioma cells' ability to invade and migrate [54]. The development of high-grade glioma may also be influenced by additional unidentified targets that might be impacted by the reduced expression of ADAR [37]. The breaking of miRNA duplexes during maturation is another source of alternative miRNA transcripts. These duplexes undergo cleavage to produce a mature, functional miRNA that joins the RISC and a miRNA* that is often destroyed after cleavage. On the other hand, research found that miRNA transcripts are functional and may inhibit the translation of mRNA targets, which may have an impact on the pathophysiology of the illness [55]. Even while miRNAs target distinct signaling pathways, their combined impact may be responsible for a tumor's shared feature. For instance, miR-107, miR-130b, and miR-23b all play a part in invasion but control distinct signaling pathways. This highlights the intricacy and significance of miRNAs in the biology of gliomas, and changed expression profiles may provide vital details about a particular tumor. Notch2 was shown to be a crucial target in a recent investigation on the function of miR-107 in glioma migration and invasion [56, 57]. In gliomas, miR-107 is downregulated, and in glioma cell lines, overexpression of miR-107 resulted in the downregulation of Notch2, which regulates a number of properties of tumors, including migration. The study concluded that downregulation of miR-107 in glioma promotes migration and invasion through Notch2 signaling pathways [56]. Additionally, a comparison of miRNA expression profiles in migratory and migration-restricted groups of glioblastoma cell lines revealed miR-23b as a regulator of both migration and invasion. Cell migration and invasion are caused by upregulating the non-receptor tyrosine kinase Pyk2, which is induced by downregulating miR-23b. It was determined that identifying miRNAs that are important in controlling glioma invasion may provide targets for modification to lessen invasion and enhance glioma therapy results [58]. Several investigations have been carried out to investigate the expression profiles and roles of miRNAs in GBM in an effort to get important knowledge to tackle this difficult illness. Møller *et al.* conducted a recent systematic review [59]. It was shown that an increase in miRNA expression is the most common aberration in GBM. In particular, as compared to normal brain tissue, miRNAs 256, including miR-10b, miR-17-92 cluster, miR-21, and miR-93, were considerably overexpressed in GBM, while 95 miRNAs, including miR-7, miR-34a, miR-128, and miR-137 were significantly underexpressed. Furthermore, distinct miRNAs have been linked to various glioma stages. When the miRNA expression profiles of WHO grade II gliomas were analyzed, it was found that two miRNAs (miR-184 and miR-328) were downregulated during progression, while 12 miRNAs (miR-9, miR-15a, miR-16, miR-17, miR-19a, miR-20a, miR-21, miR-25, miR-28, miR-

130b, miR-140, and miR-210) were upregulated [60]. Additional research has also shown differently expressed miRNAs in the latter stages of GBM, including overexpression of miR-182 and downregulation of miR-137 [61]. Significantly, miRNAs are essential for controlling proliferation, differentiation, and apoptosis because they preferentially target genes involved in development. This suggests that, within the framework of cancer pathobiology, miRNAs impact several critical aspects of cancer [62]. In fact, it has been shown that miRNAs support replicative immortality, robust proliferative signaling, evasion of growth suppressors, resistance to cell death, induction of angiogenesis, and activation of invasion and metastasis. Furthermore, miRNAs are important regulators of treatment resistance in GBM.

7. CIRCULATING miRNA AS GLIOMA BIOMARKERS

Tumor indicators such as circulating nucleic acids and circulating tumor cells are often used to forecast treatment results and track therapeutic responses. It may be difficult to use imaging to diagnose GBM since treatment response often results in increased absorption of contrast medium, which can be misinterpreted as pseudoprogression of the illness [63, 64]. It's critical to distinguish between real advancement and pseudoprogression in order to maximize patient treatment. Circulating biomarkers can be found in CSF fluid and blood, and important glioma mutations like IDH1/IDH2 may be found in circulating DNA [65]. Circulating tumor cells are uncommon in gliomas, nonetheless, and current technology does not guarantee their therapeutic use. Likewise, serum proteomics has not yet yielded data that are therapeutically meaningful [66]. Because extracellular vesicles (EVs) contain a variety of chemicals that are shielded from destruction, they are a promising source of circulating biomarkers [67]. All cells emit EV to allow nonadjacent cells to communicate with one another, and cancer cells produce EV in response to a variety of stressors, such as therapy [68]. Interestingly, EVs are a perfect source of circulating biomarkers since they are selectively loaded, and their composition reflects the biology of the donor cells [69]. While EV usage in clinical settings is still in its infancy, two small studies utilizing GB have shown encouraging outcomes. In one of these studies, the amounts of the DNA repair enzymes MGMT and APNG in the parent tissue and EV were compared before and after TMZ therapy [70]. In the second research, exosome mRNA was used to look into immunological markers and cytokines that changed after glioblastoma patients received a tumor vaccination [71]. Both investigations point to the potential use of EV-transported compounds in the development of accurate tests for tracking glioblastoma disease progression. Numerous investigations have examined the amounts of certain circulating miRNAs known to be involved in glioma tumors or reported miRNA profiling in the plasma of individuals with this malignancy. A comprehensive literature review found eleven miRNAs with a limited signature, and this information was used to screen a small group of GBM patients. The findings demonstrated that the expression levels of miR-125b and miR-497 may distinguish between high- and low-grade gliomas [72]. By tracking the development of primary low-grade gliomas into secondary GBM, these markers may prove to be very valuable in enabling more precise treatment procedure scheduling. Numerous researches have looked at deregulated miRNAs in GBM as circulating biomarkers. For instance, it was discovered that the plasma of glioblastoma patients had higher levels of miR-21 than that of normal controls, yet the same patient group had lower levels of miR-128 and miR-3423p. Following therapy, these miRNAs' expression levels went back to baseline, indicating that they may be used to track disease response and recurrence [73]. Interestingly, a signature that predicts overall survival and disease-free status independently of other clinical variables was found in a recent miRNA profiling research of a large population of glioblastoma patients [74]. In summary, there is compelling evidence that circulating biomarkers may be useful in clinical settings and be able to capture the molecular complexity of GBM. However, before liquid biopsies may be used routinely in clinical settings, additional useful biomarkers are required to provide trustworthy and repeatable tests.

8. microRNA THERAPEUTICS FOR GLIOBLASTOMA

miRNAs are a class of endogenously generated RNA molecules with a function in RNA interference (RNAi). The pathophysiology of GBM and tumor plasticity are both heavily influenced by miRNAs (Table **1**). Researchers have shown that miRNA expression varies not only across different kinds of gliomas but also within the same tumor between distinct cell subpopulations [29]. Alterations in miRNA expression may be used as indicators for diagnosis and prognosis [75]. MiRNAs' therapeutic benefits stem from their ability to target many genes involved in a wide range of physiological processes. By increasing the expression of ts-miRNAs like miR-128-3p or miR145-5p in GBM, it may be possible to selectively downregulate several genes involved in cell proliferation, self-renewal, invasion, metastasis, angiogenesis, and treatment resistance [76]. MiRNAs' therapeutic benefits stem from their ability to target many genes involved in a wide range of physiological processes. By increasing the expression of ts-miRNAs like miR-128-3p or miR145-5p in GBM, it may be possible to selectively downregulate several genes involved in cell proliferation, self-renewal, invasion, metastasis, angiogenesis, and treatment resistance [77]. Over the last several years, researchers have uncovered a wealth of information on miRNAs and their function as oncogenes or tumor suppressors in glioma. Glioma tumorigenesis is a good example of how a single miRNA may have a wide variety of effects on different targets. By regulating multiple targets, miRNAs like miR-128-3p and miR-145-5p have a wide range of anti-tumorigenic effects in GBM, including induction of apoptosis and senescence, suppression of invasive, metastatic, and angiogenesis potential, and relief of drug resistance [78]. Tumor regression in cancer cells and, in the instance of miR-10b in GBM, complete tumor eradication may result from suppressing the expression of oncogenic miRNAs like miR-21-3p and miR-21-5p [79]. Additionally, primary glioma cells that paracrinely expressed the miR-302-367 suppressed the stemness, proliferation, and tumorigenicity of adjacent GBM cells (Fig. **1**) [80].

Table 1. Altered expression of a number of oncogenic and suppressor microRNAs in glioblastoma.

MicroRNA	Pattern of expression (Up/ Down)	Target/Regulator	Function	Reference
Oncogenic miRNAs				
miR-21	Up	PTEN MPS1	Downregulation of PETEN, tumor growth, Rescued cell growth from MPS1 inhibition	doi: 10.1016/j.biomaterials.2019.02.016 doi: 10.18632/oncotarget.4143
miR-221	Up	SOCS3	Increase in the invasion, proliferation, migration, angiogenesis	doi: 10.1002/jcp.28794.
miR-4516	Up	PTPN14	Proliferation and invasion of GBM cells	doi: 10.1038/s41388-018-0601-9
miR-299-5p	Up	MAPK	Activation in the MAPK pathway and cell proliferation, invasion	doi: 10.1042/BSR20181051
miR-378	Up	VEGFR2	Promotion in tumor growth, angiogenesis	doi: 10.1042/BSR20181051
miR-10b	Up	TGF-β	Promotion in the cell proliferation, migration	doi: 10.3892/ijo.2017.3947. Epub 2017 Apr
miR-29a	Up	PTEN AKT	Promotion in the glioblastoma cell growth and invasion	doi: 10.1016/j.biopha.2017.01.137
miR-595	Up	Cyclin D1 SOX7	Increase in glioblastoma cell proliferation and colony formation	doi.org/10.1016/j.biopha.2016.03.008
miR-210	Up	caspase-8 associated protein 2 (CASP8AP2)	inhibition of apoptosis	doi: 10.1074/jbc.M109.020925
miR-25	Up	CDKN1C p27 Cell adhesion molecule 2	Promotion in cell proliferation, migration and invasion	doi: 10.1016/j.biopha.2015.02.005 doi: 10.3892/etm.2021.10938
miR-155	Up	VHL MYC	Angiogenesis and microvascular proliferation cell proliferation	doi: 10.1371/journal.pone.0083055.
Suppressor miRNAs				
miR-29	Down	SREBP1	Lipid synthesis and GBM cell growth	doi: 10.1016/j.celrep.2016.07.017
miR-34a	Down	MYCN	GBM cell proliferation, invasion, migration, and tumorigenesis	doi: 10.1158/0008-5472.CAN-09-0529
miR-219	Down	EGFR	Promotion in glioblastoma cell growth	doi: 10.1016/j.neuron.2010.01.027

(Table 1) contd…

MicroRNA	Pattern of expression (Up/ Down)	Target/Regulator	Function	Reference
miR-7	Down	EGFR	Promotion in tumor growth	doi: 10.1158/0008-5472.CAN-07-6639
miR-340	Down	GSK3β	Increase in cell proliferation, colony formation	doi: 10.18632/oncotarget.6968
miR-577	Down	Axin2, c-myc, β-catenin	Increase in expression of the Wnt signaling pathway gene, cell growth	doi: 10.1002/mc.22304. Epub 2015 Mar 12
miR-186-5p	Down	Twist1	Increase in the cell proliferation	doi: 10.3892/mmr.2019.10207

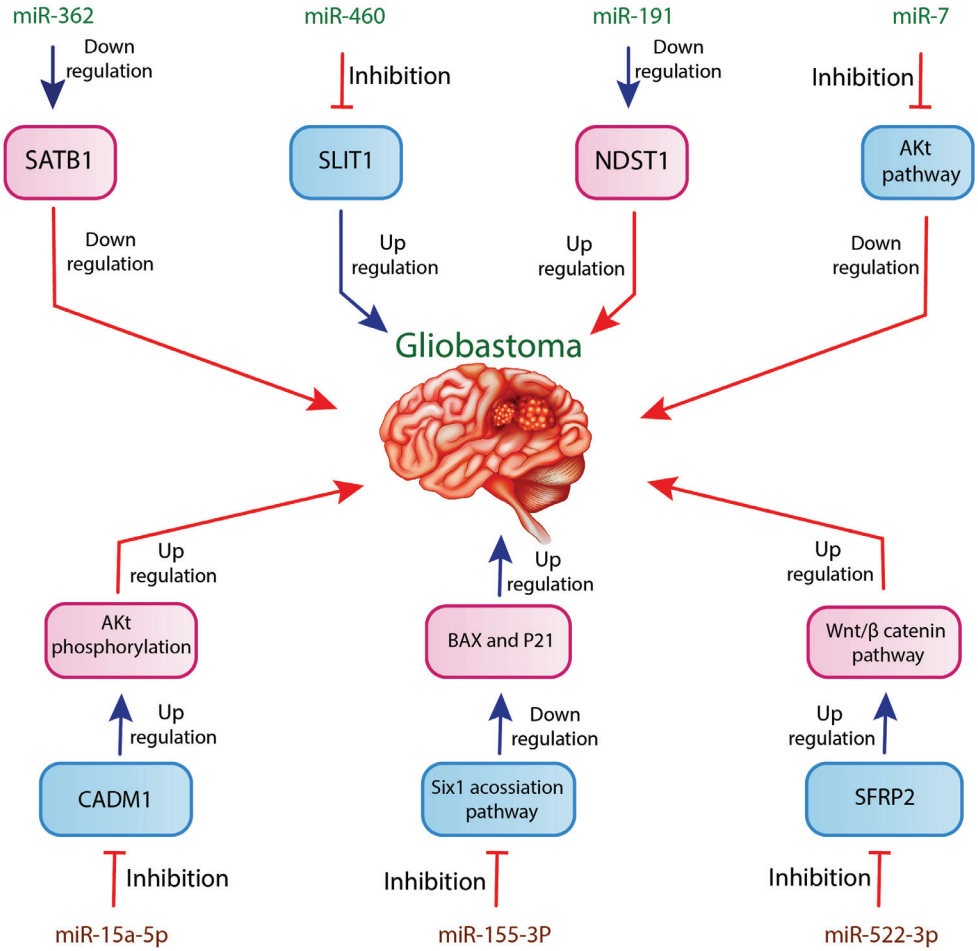

Fig. (1). miRNAs interaction with signaling pathways involved in the pathogenesis of glioblastoma. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

9. microRNAs AND METASTASIS IN GLIOBLASTOMA

An essential miRNA that has been linked to a number of cancers is miR-376a-3p. Elevated levels of miR-376a-3p in the cytoplasm or nucleus have been linked to more aggressive tumors, suggesting that miR-376a-3p may be a useful prognostic indicator for glioma patients [81]. KLF15 has been shown to be the downstream gene that interacts with miR-376a-3p based on bioinformatics investigation. A class of transcription factors called Krüppel-like transcription factors (KLFs) has a zinc finger domain (C_2H_2). These components, which include nine different proteins that add up to eighteen KLF members, are present in a variety of eukary-

otes. The immunological, respiratory, and hematopoietic systems are all regulated by KLF15. Furthermore, regulating downstream gene expression contributes to the growth of tumors. MiR-376a-3p has been shown by Chen *et al.* to be involved in controlling the glioma cells' motility and invasiveness. Additionally, they suggested a number of possible methods [82]. MiR-623 expression has been seen to be downregulated in a number of cancer types, including stomach and lung cancer. It has been shown that this miRNA acts as a tumor suppressor gene [83]. MiR-623 mimics can inhibit glioma cell formation, invasion, development, and migration, as shown by prior research. Furthermore, when a medication aimed at upregulating the expression of miR-940 was given to a mouse model of an intracranial xenograft, the tumor's size was markedly decreased. These results suggest that miR-940 may be taken into account as a possible glioma treatment [84]. Moreover, the number of miRNAs associated with metastasis in GBM patients is constantly expanding. MiR-382 is one such miRNA that prevents GBM from spreading and progressing. MiR-382 targeting seems to be a viable approach to improve GBM treatment efficacy [85]. TRIM44, a member of the TRIM family of proteins, plays a role in several disorders, such as viral infections, developmental abnormalities, and neurodegenerative diseases [83]. Their structure has an E3 site, which permits post-translational regulation of E3 ubiquitin ligase activity. Prior research has shown that TRIM44 is overexpressed in a variety of malignancies, which stimulates the growth, division, and advancement of the cell cycle. Furthermore, overexpression of TRIM44 may improve the invasion and migration of cancer cells and raise the likelihood that malignancies will metastasize [86]. In conclusion, TRIM44 expression inhibition may be helpful in controlling tumor spread and regulating tumor development. Using RT-PCR, research was carried out to assess the expression levels of miR-623 in GBM tissue. The influence of miR-623 upregulation on malignant cell invasion, migration, and proliferation was further investigated by means of transwell, colony formation, and MTS tests. Moreover, a subcutaneous mouse xenograft model was used to assess the effects *in vivo*. Using western blotting and a dual-luciferase reporter assay to verify miR-623TRIM44 binding, the effects of miR-623 on epithelial-to-mesenchymal transition (EMT) markers were evaluated. Notably, it was shown that GBM patient samples and cell lines had downregulated miR-623. TRIM44 suppression or overexpression of miR-623 substantially blocked the migration, invasion, and proliferation of GBM cells. On the other hand, enhanced TRIM44 expression, EMT, and the consequent advancement of GBM were the outcomes of miR-623 suppression. The direct binding of miR-623 to the 30 UTR region resulted in the suppression of TRIM44 expression. Furthermore, in nude mice with a GBM xenograft, systemic treatment of miR-623 mimics reduced tumor formation and lowered TRIM44 protein expression. The proliferation and migration of the glioma cell lines U251MG and LN229 were likewise shown to be suppressed by high expression of miR-623 or low expression of TRIM44, as confirmed by the researchers. They concluded that miR-623 was a viable therapeutic target for the treatment of GBM because it could effectively reduce EMT caused by TRIM44 by directly targeting the TRIM44 30 UTR (Figs. **2, 3**) [87].

10. COMBINATION THERAPY USING NATURAL COMPOUNDS FOR GLIOBLASTOMA

Multimodal treatment is the most effective strategy for glioblastoma. These strategies include combining several therapeutic agents or therapies, each of which works in a slightly different way to kill cancer cells. However, the discovery of optimum natural compounds or pharmaceutical combinations is essential for the development of successful targeted therapy for glioblastoma. Because of this, modern techniques, such as system biology and computational tools for large-scale genomics, need to be used [88]. Resveratrol is a natural polyphenol that may be found in peanuts, grapes, and mulberries [89]. Showed that resveratrol's ability to overcome TMZ resistance involves a mechanism reliant on nuclear factor kappa B. The enzyme O (6)-methylguanine-DNA methyltransferase (MGMT) is affected by resveratrol and TMZ in T98G glioma cells. In addition, it boosted apoptosis by increasing NF-B cleavage intracellular content reduction and nuclear translocation. Chromatin aggregation and nuclear condensation were also induced. The expression of the astrocyte differentiation marker glial fibrillary acid protein (GFAP) was increased, and the expression of matrix metalloproteinase-9 (MMP-9) was reduced in xenograft glioblastoma cells, according to a separate study conducted at the same time. In addition, this therapy promotes the production of reactive oxygen species, which acts as a downstream signal for the activation of AMP-activated protein kinase. The combined anti-proliferation effects are due in part to the fact that active AMPK blocks mTOR signaling and decreases antiapoptosis protein Bcl2 [90]. The glioblastoma suppressor microRNA (miR-7-1-3p) and the apoptotic pathway have both been demonstrated to be induced by a combination of silibinin and luteolin [91]. According to the findings of Bai *et al.*, silibinin not only inhibits the metabolic pathway but also causes apoptosis in glioblastoma cells *via* controlling the levels of caspase3 and PARP-1. Silibinin is a dual-specific STAT3 inhibitor [92]. This research indicates represents a promising avenue for treating glioblastoma. Not all silibinin formulations are equally effective in penetrating the brain's blood-brain barrier and reaching their intended cancerous tissue targets [93].

11. NATURAL COMPOUNDS MODULATING THE FUNCTION OF EFFLUX TRANSPORTERS

Brain tumor tissue has a decreased drug concentration due to the presence of efflux transporters, including P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in the blood-brain barrier (BBB). Some natural compounds have been shown to have chemosensitizing effects by competitively inhibiting these efflux transporters [94-96]. Flavonoids like silymarin and Biochanin A block P-gp substrate binding, which in turn increases the cytotoxic action of doxorubicin, daunomycin, and vinblastine (Fig. **2**) [97]. BCRP, coupled with the P-gp efflux transporter, has been shown to be present in glioblastoma cell lines. The efflux process at the BBB mediated by BCRP and P-gp proteins is critical to the failure of glioma therapy. The role of this efflux in fostering drug resistance is equally substantial. The most popular method of overcoming these obstacles is to use efflux transporter inhibitors along with

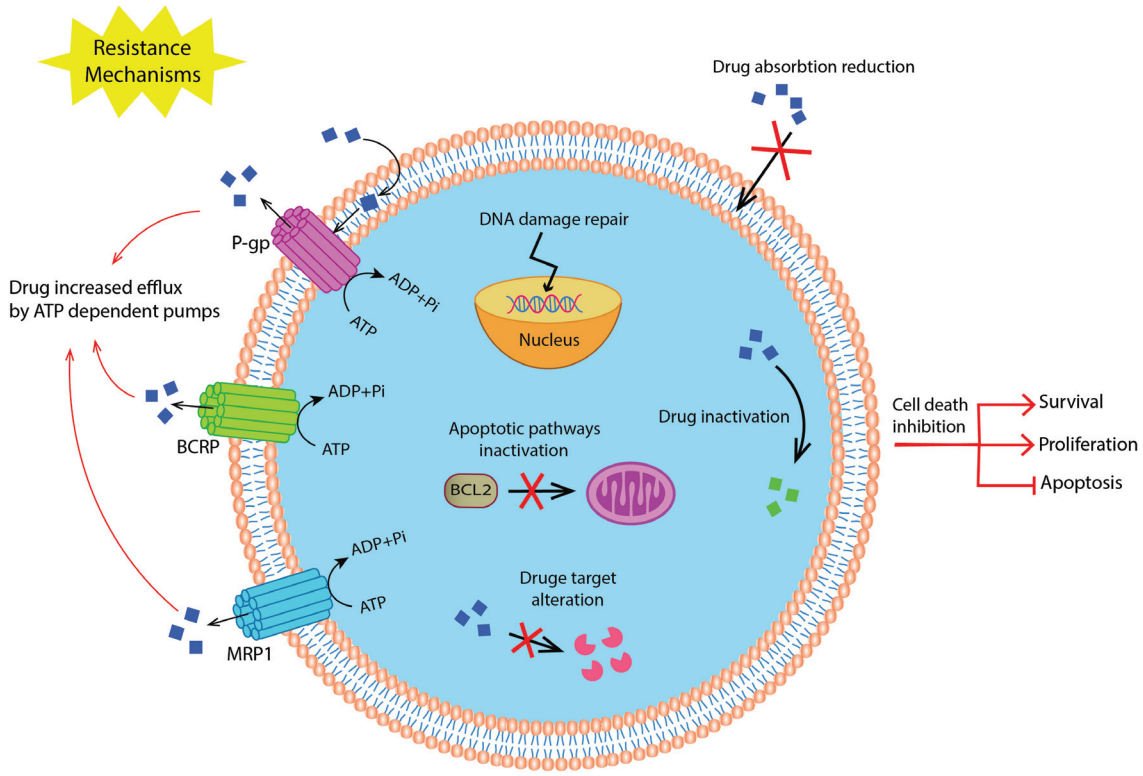

Fig. (2). modulating the function of efflux transporters. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

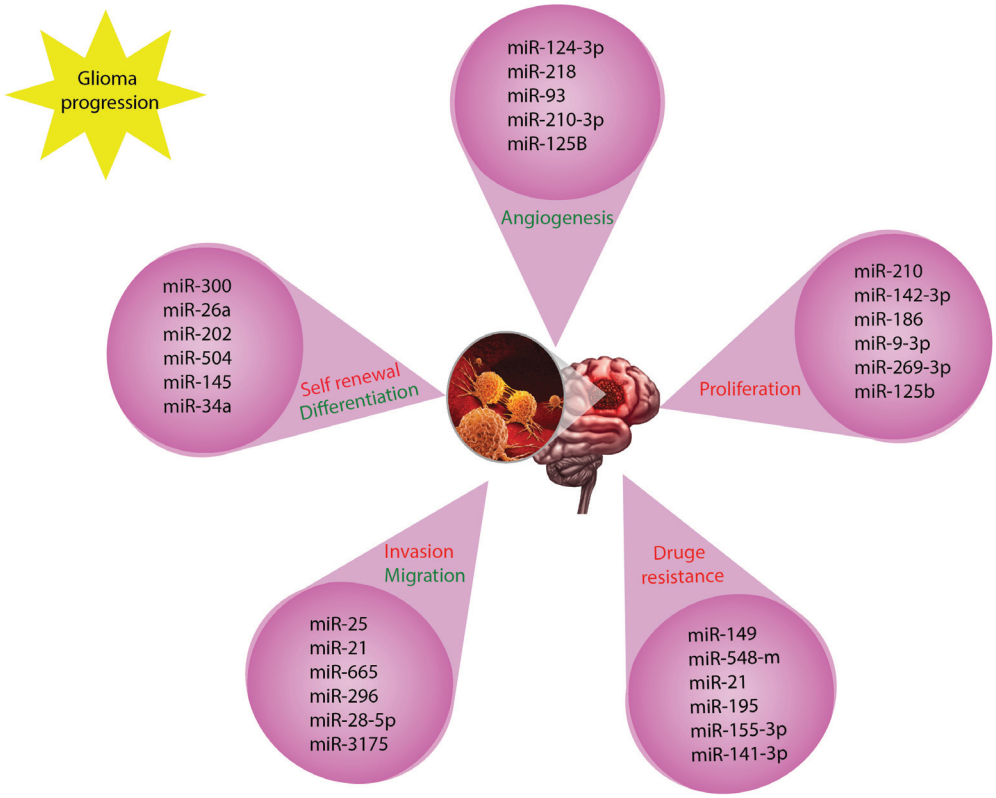

Fig. (3). Key miRNAs involved in the pathogenesis of glioblastoma. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

chemotherapeutic drugs [98, 99]. The usage of glyceollin, which inhibits multidrug resistance protein2 and brain-circumscribed resistance protein (BCRP), might have a profound influence on medication absorption in the brain [100].

12. NATURAL COMPOUNDS WITH DIRECT ANTI-GLIOMA

In order to overcome the BBB's barrier and reach sufficient drug concentration in tumor tissue, medicines are often administered at greater concentrations in glioma therapy [101]. However, the increased medication concentration causes organ damage [102]. Many naturally occurring substances have been shown to have anti-glioma properties, including those that block cell cycle progression (neurostatin), induce apoptosis (cannabis), and modulate inflammatory factors (retinoids) [101]. Several other natural substances have been shown to encourage anti-glioma efficacy. Among their many effects on gliomas are the activation of apoptosis, modulation of reactive oxygen species (ROS) production, intracellular pathway targeting, cell cycle arrest, and suppression of migration and invasion. Many natural substances have been found to have anti-glioma effects by either directly changing the balance of apoptotic and antiapoptotic pathways or by indirectly impacting these pathways. Apoptosis is the most important type of cellular death in glioma. Extract from sea buckthorn causes apoptosis in the C6 cell line. By reducing ROS production and increasing Bax expression, it slows cell development. It controls protein expression by also being nuclearly localized. 1′-deoxyrhodoptilometrin is a marine-derived compound that induces cell death in glioma and colon cancer. Multiple targets, including IGF1 receptor kinase, FAK, and EGFR, are affected, and ERK phosphorylation is controlled [103].

13. EFFECTS OF NATURAL PLANT PRODUCTS ON microRNA

Small non-coding RNAs known as miRNAs are present in both invertebrates and vertebrates. These miRNAs regulate the expression of genes through sequence complementation. They consist of 19–25 nucleotides in length [104]. They are involved in several physiological processes, including metabolism, cellular development and differentiation, and apoptosis, and play a crucial function in biology by inhibiting gene expression after transcription has taken place. MiRNA expression is a key mechanism in tumor genesis and progression. Changing the expression of miRNAs is a novel strategy for treating cancer, and recent research on plant-based compounds has shown that this can be done [105]. MicroRNA-16 has been recognized as a crucial regulator in cancers of various sources by a number of studies [106]. It has been shown that microR-16 plays a crucial role as a cancer suppressor gene in glioblastoma development, migration, and invasiveness and that microR-16 regulates these processes in a new manner by inhibiting the nuclear factor-B1/MMP-9 signaling pathway [107]. The expression of the tumor suppressor microRNA-16 was upregulated, and the production of matrix metalloproteinase-9 (MMP-9) was downregulated in U87 glioblastoma cells after treatment with the natural coumarin osthole [108]. Therefore, more investigation is required to determine whether or if apoptosis triggered by osthole is mediated by the downregulation of matrix metalloproteinases. Upregulation of miR-128, a miRNA highly expressed in the brain, suppresses glioma cell growth [109] and has been shown to be a direct target of miR-128 and is the transcription factor E2F3a. There is a complementary 5′-end to miR-128. DNA methylation, change in chromatin structure by miRNAs, and post-translational modifications to histone that may degrade mRNA or modify their translation are the key epigenetic processes that affect gene expression. Inhibition of the 3′-UTR of E2F3a, which facilitates post-transcriptional negative regulation of E2F3a by RNA duplex formation, is an example of how plants and their products may influence epigenetic pathways (solid arrow indicates regulation). Phanax ginseng's ginsenoside Rh2 promoted miRNA-128 expression, which in turn suppressed E2F3a synthesis and halted glioblastoma cell growth [110]. Target genes for miRNAs are implicated in the cell cycle and apoptotic pathways; Olea europaea leaf extract has a miRNA regulating impact, influencing the expression of miRNAs such miR-153, miR-137, miR-145, miR-181b, and let-7d. Olea europaea leaf extract inhibits the proliferation of glioblastoma cells (T98G, U-138MG, and U-87MG) by upregulation of certain miRNAs. Olea europaea leaf extract and temozolomide showed a synergistic effect when used together [111].

14. NATURAL COMPOUNDS WITH DIRECT ANTI-GLIOMA ACTIVITY

Drugs are usually given at a greater dosage while treating gliomas in order to get past the obstacles presented by the BBB and guarantee adequate drug levels in the tumor tissue [112]. However, toxicity in other human organs is often the result of this elevated drug concentration [113]. Currently, studies are being conducted to determine if natural substances are useful in glioma treatment. Perillyl alcohol is one such substance that may be found in the essential oils of plants like citrus fruits and lavender. Regarding its potential to combat gliomas, a Phase I/ II trial produced encouraging findings. Furthermore, perillyl alcohol delivered *via* the nose helps get beyond the blood-brain barrier, removing the need for oral administration and all of its negative side effects, including mucositis and myelosuppression. Perillyl alcohol targets TGF-β, NF-κB, and other cell cycle proteins in addition to suppressing Ras protein; these actions all contribute to its anticancer effect [114]. Various natural drugs have shown anti-glioma properties. These chemicals include genistein, which modulates tyrosine kinase signaling pathways; neurostatin, which inhibits the cell cycle; cannabis, which induces apoptosis; and retinoids, which modulate inflammatory factors [112]. Numerous organic substances have shown encouraging efficacy in combating gliomas. They work *via* a number of methods, including triggering apoptosis, controlling the production of ROS, focusing on intracellular pathways, causing cell cycle arrest, and preventing migration and invasion. Glioma cell death is primarily caused by apoptosis, and a variety of naturally occurring substances have been shown to exhibit anti-glioma activity. These compounds either directly alter the equilibrium between apoptotic and antiapoptotic factors or regulate the pathways that are involved in this equilibrium. For instance, it has been shown that sea buckthorn extract causes apopto-

sis in the C6 cell line. Decreasing ROS production and raising Bax expression in a dose-dependent way prevents the development of cells. Furthermore, it localizes to the nucleus to control the expression of proteins [103]. Deoxyrhodoptilometrin, derived from marine sources, causes necrosis and apoptosis in colon and glioma cells. It targets several proteins, including FAK, EGFR, and IGF1-receptor kinase. It also controls the phosphorylation of ERK. Fascaplysin, another alkaloid, also has anticancer action by causing glial tumors to undergo apoptosis [115]. One common dietary ingredient that has potent anticancer effects is curcumin. It functions by focusing on NF-κB, which results in caspase-mediated apoptosis by suppressing Bcl2 and Bcl-xl [116]. It has been discovered that chokeberry extract, which includes anthocyanins, causes necrotic cell death in the U373 cell line. Furthermore, downregulation of MMP-2, MMP-14, MMP-16, and MMP-17 has been found. It could have a synergistic impact when used with curcumin. 2-By controlling apoptotic and antiapoptotic proteins, 2-dihydroailanthone causes apoptotic cell death and cell cycle arrest in U251 cells. It has been discovered that α-Bisabolol, a naturally occurring essential oil, demonstrates cytotoxicity by causing apoptotic cell death in glioma cell lines from rats and humans. Researchers observed breakage of poly (ADP-ribose) polymerase, DNA laddering, and release of Cytochrome C in α-bisabolol-treated cells [117].

15. CURCUMIN

Small non-coding RNAs known as miRNAs are important in the development of cancer [118]. Turmeric's curcumin component has been shown to target miRNAs and have anticancer actions. Numerous studies have shown that curcumin may influence the production of certain miRNAs, including miRNA-34a, miRNA-21, miRNA-181, miRNA-7, miRNA-9, and miRNA-200c, that are implicated in processes connected to cancer [119]. Additionally, curcumin has been shown to target miRNAs such as miRNA-186, miRNA-21, and miRNA-27a, which in turn affects how sensitive cancer cells are to chemotherapy. Chemotherapy-resistant GBM is a kind of brain tumor where drug efflux pumps are overexpressed [120, 121]. The use of miRNAs to control drug efflux and chemoresistance in GBM cells has been studied recently. Munoz *et al.*, for example, looked into the delivery of anti-miRNA-9 to GBM cells using exosomes made from mesenchymal stem cells (MSC). The scientists discovered that blocking miRNA-9 made GBM cells more susceptible to treatment, as seen by increased caspase activity and apoptosis [120]. miRNA-21 is an additional miRNA linked to resistance to chemotherapy [122].

16. GREEN TEA

Apart from herbal tea, which isn't made from the Camelia sinensis shrub, tea is a widely consumed beverage around the globe. The degree to which the leaves have oxidized determines the kind of tea. For instance, green tea is the least processed as it is prepared from unoxidized leaves. Green tea has many polyphenols and antioxidants as a consequence. Epigallocatechin (EGC) and epigallocatechin-3-gallate are the main polyphenolic components in green tea (EGCG). With strong anticancer characteristics and action against neuroblastoma, EGCG is the most well-known polyphenol [123]. Chakrabarty *et al.* found that these polyphenolic components interact with miRNAs to carry out their anticancer activity in two consecutive trials. In neuroblastoma cell lines, it was shown that EGC and EGCG differently control six distinct miRNAs. They reported that when treating these two polyphenols independently, they saw three oncogenic miRNAs being downregulated (miR-92, -93, and -106b). Three tumor suppressor miRNAs (miR-7-1, 34a, and -99a) were upregulated in response to treatment with EGC and EGCG [124].

17. PANAX GINSENG

A perennial plant called Panax ginseng is well-known for its ginseng-like root. It is often found growing in East Asian mountains and is an essential component of traditional Chinese, Japanese, and Korean medicine. Ginsenoside Rh2, a triterpene saponin, is the most important secondary metabolite found in ginseng. This molecule is made up of a sugar component and a steroid nucleus. Ginsenoside Rh2 has a number of noteworthy properties, including the ability to lower blood glucose, prevent ischemic brain damage, and inhibit the growth of glioma cells [125]. In order to work, it controls the expression of miRNAs. According to Wu *et al.*, ginsenoside Rh2 enhanced the expression of many miRNAs, including miR-125, Let-7c/d, -129, -181a/b/c, and -128. Nevertheless, miR-128 showed the most alteration. Glioma cell proliferation was inhibited, and miR-128 was upregulated in response to ginsenoside Rh2 treatment. MiR-128 induction prevents the growth of glioma cells by triggering caspase-3 and preventing transcriptional activation of E2F3a [126].

18. APIGENIN

Apigenin is a flavonoid that occurs naturally in a variety of plants and is sometimes referred to as 5,7-trihydroxyflavone. It is mostly present in tea leaves, although it is also present in fruits, vegetables, and legumes [127]. Numerous research works have examined the various biological characteristics of apigenin, such as its antiviral, immunomodulatory, anti-inflammatory, and anticancer effects [128]. The effects of apigenin on glioma cells were investigated by Chen *et al.* They discovered that apigenin administration resulted in glioma cell death and inhibition of cell growth, with miR-16 being upregulated in particular. Through the inhibition of BCL2 and NF-κB signaling pathways, it was shown that the induction of miR-16 inhibited the proliferation of glioma cells. As a result, apigenin may be used as a therapeutic option for the treatment of a variety of brain conditions, including brain cancer [129].

19. LUTEOLIN

Flavonoids like luteolin, also known as 30,4',5,7-tetrahydroxyflavone, are present in fruits, vegetables, and certain medicinal plants. Numerous biological actions, including anti-inflammatory, antioxidant, and anticancer properties, have been described for it. Lutein has been shown in several studies to be a neuroprotective agent [130]. According to research, luteolin may stimulate neurite extension and

differentiation in PC12 cells *via* the ERK and protein kinase C (PKC) pathways, indicating that it is a neurotrophic factor. Subsequent research revealed the role of miRNA (miR-132) in PC12 cell differentiation mediated by luteolin. Lutein treatment causes ERK to become phosphorylated, which then phosphorylates cAMP Response Element-Binding Protein (CREB). Pre-synthesis miR-132's is mediated by CREB, which also upregulates the expression of the precursor by translocating to the nucleus and binding to CRE (cAMP response element). This aids in nerve cell development and neurite extension. Lutein-mediated differentiation therapy has the potential to be investigated as a therapeutic approach against several forms of brain cancer since it induces the differentiation of nerve cells and upregulates miR-132 [82].

20. RESVERATROL

Resveratrol, also known as 3,5,40-trihydroxytrans-stilbene, is a typical polyphenolic phytoalexin that may be eaten. It can be found in a few other food sources, grapes, peanuts, and red wine. It has unusual therapeutic potential. Its role is to prepare for certain age-related diseases, such as cancer, neurological diseases, and cardiovascular diseases [131]. It also has antioxidant and anti-inflammatory qualities [132]. It has a well-established pathophysiological involvement in neurodegenerative diseases such as Alzheimer's disease (AD) and brain cancers like glioblastoma [133]. According to a number of studies, resveratrol may control the expression of miRNAs, which are shown to be dysregulated in glioblastoma or AD. Overexpression of miR-21, which is known to have antiapoptotic properties, is seen in glioblastoma. It reduces the expression of NF-κB by inhibiting both LRRFIP1 and the synthesis of LRRFIP1 [134]. In glioblastoma cells, downregulation of miR-21 resulted in decreased cellular growth and apoptosis [135]. According to Li *et al.*, resveratrol therapy downregulated the expression of miR-21, which in turn caused glioblastoma cells to proliferate less rapidly and undergo accelerated apoptosis. Resveratrol affects miRNAs implicated in AD regulation in addition to glioblastoma. There have been reports of increased miRNAs in AD, such as miR-146a, -155, -21, and -125b, which cause neuroinflammation. In AD, tau-hyperphosphorylation is mediated by miR-15b. Moreover, downregulation of miR-9, -29c, -186, -107, and -29a occurs in AD and influences the activity of BASE1 (β-site APP cleaving enzyme 1, also known as β-secretase). Since BASE1 abnormally produces Aβ plaques, this protease enzyme is presently the focus of AD research. Resveratrol therapy reverses the expression of all these miRNAs, slowing the course of the illness. It has been suggested that resveratrol is beneficial in treating neurological conditions such as brain cancer. As a result, it may be a useful treatment choice for a range of brain diseases. According to Li *et al.*, resveratrol therapy downregulated the expression of miR-21, which in turn caused glioblastoma cells to proliferate less rapidly and undergo accelerated apoptosis. Resveratrol affects miRNAs implicated in AD regulation in addition to glioblastoma. There have been reports of increased miRNAs in AD, such as miR-146a, -155, -21, and -125b, which cause neuroinflammation. In AD, tau-hyperphosphorylation is mediated by miR-15b. Moreover, downregulation of miR-9, -29c, -186, -107, and -29a occurs in AD and influences the activity of BASE1 (β-site APP cleaving enzyme 1, also known as β-secretase). Since BASE1 abnormally produces Aβ plaques, this protease enzyme is presently the focus of AD research. Resveratrol therapy reverses the expression of all these miRNAs, slowing the course of the illness. It has been suggested that resveratrol is beneficial in treating neurological conditions such as brain cancer. As a result, it may be a useful treatment choice for a range of brain diseases. According to Li *et al.*, resveratrol therapy downregulated the expression of miR-21, which in turn caused glioblastoma cells to proliferate less rapidly and undergo accelerated apoptosis. Resveratrol affects miRNAs implicated in AD regulation in addition to glioblastoma. There have been reports of increased miRNAs in AD, such as miR-146a, -155, -21, and -125b, which cause neuroinflammation. In AD, tau-hyperphosphorylation is mediated by miR-15b. Moreover, downregulation of miR-9, -29c, -186, -107, and -29a occurs in AD and influences the activity of BASE1 (β-site APP cleaving enzyme 1, also known as β-secretase). Since BASE1 abnormally produces Aβ plaques, this protease enzyme is presently the focus of AD research. Resveratrol therapy reverses the expression of all these miRNAs, slowing the course of the illness. It has been suggested that resveratrol is beneficial in treating neurological conditions such as brain cancer. As a result, it may be a useful treatment choice for a range of brain diseases [136].

CONCLUSION

In this paper, we highlighted the possible interaction between miRNAs and important natural compounds such as curcumin, resveratrol, apigenin, luteolin *etc*. The lack of symptoms until the advanced stages, along with the absence of effective treatment at this stage, requires a change of attitude in dealing with GBM. Elucidation of the crucial role of miRNAs during past research has focused attention on these non-coding RNAs to open up a new approach and attitude to the GBM dilemma. In this regard, a huge amount of attention has been attracted to natural compounds and their targets. Apart from the proposed therapeutic-diagnostic panels, in this period we need more studies on molecular mechanisms involved in the polyphenols-mediated anticancer effects to provide effective therapeutic and diagnostic panels for GBM.

AUTHORS' CONTRIBUTIONS

MR, MN, and BY wrote the article; MS and ME prepared the figures and tables; and BY and MM designed and revised it. All the authors studied and approved the final manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

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CONFLICT OF INTEREST

The author(s) declare no conflict of interest, financial or otherwise.

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