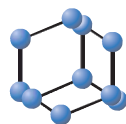


REVIEW ARTICLE

BENTHAM
SCIENCE

Polyphenols Modulate the miRNAs Expression that Involved in Glioblastoma



Maede Rezaie¹, Mohammad Nasehi², Mohammad Shimia³, Mohamad Ebrahimnezhad¹, Bahman Yousefi^{1,5,*} and Maryam Majidinia^{4,*}

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

ARTICLE HISTORY

Received: January 15, 2024
Revised: March 11, 2024
Accepted: March 16, 2024

DOI:
10.2174/0113895575304605240408105201



CrossMark

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

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 primary 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 ribonuclease 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 pri-miRNA 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 valua-

ble 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, prolifer- ation, 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 path- way 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 prolifera- tion, 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 for- mation	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 microvascu- lar 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, inva- sion, 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	GSK3 β	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

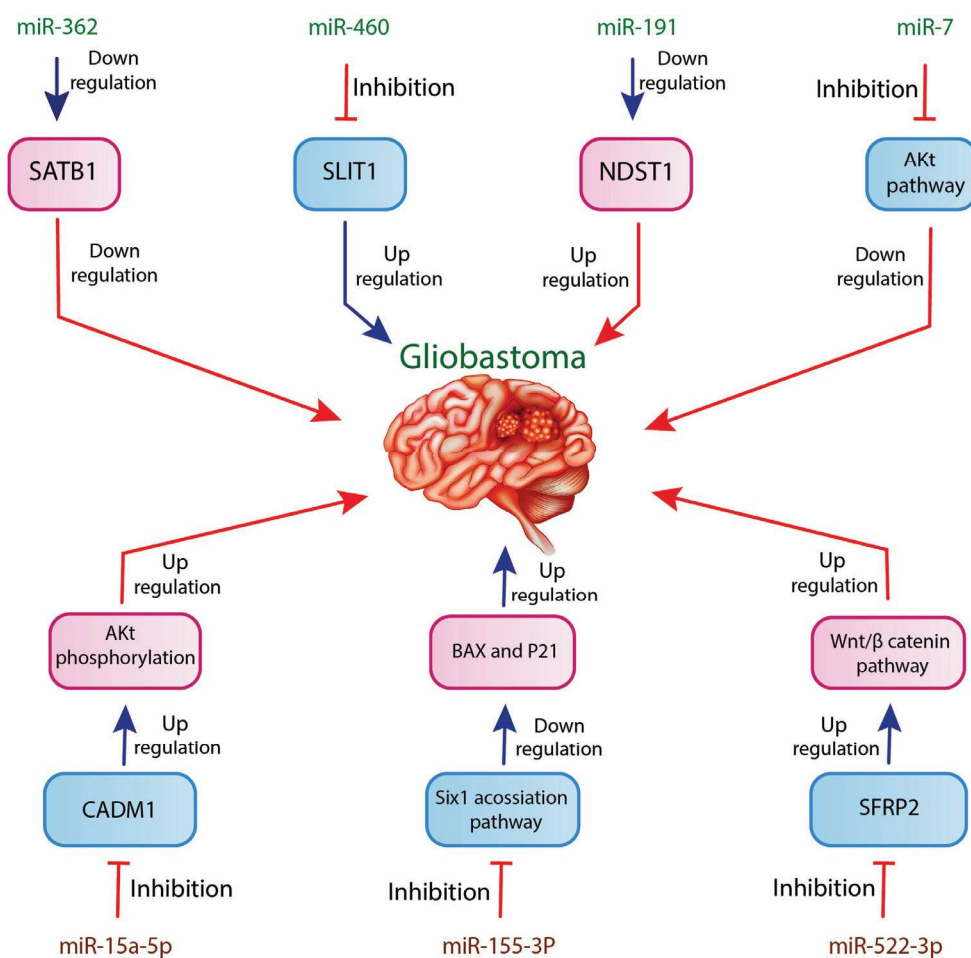


Fig. (1). miRNAs interaction with signaling pathways involved in the pathogenesis of glioblastoma. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

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 (C₂H₂). 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-623/TRIM44 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 3' 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 3' 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- κ 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

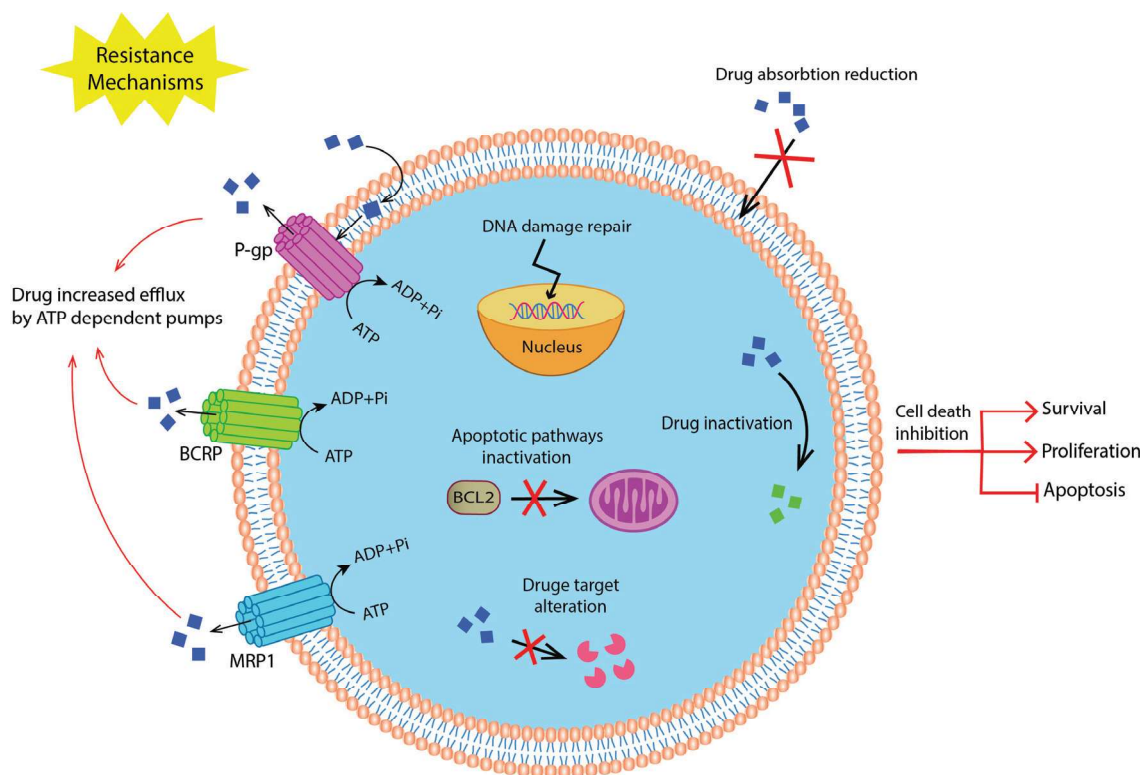


Fig. (2). modulating the function of efflux transporters. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

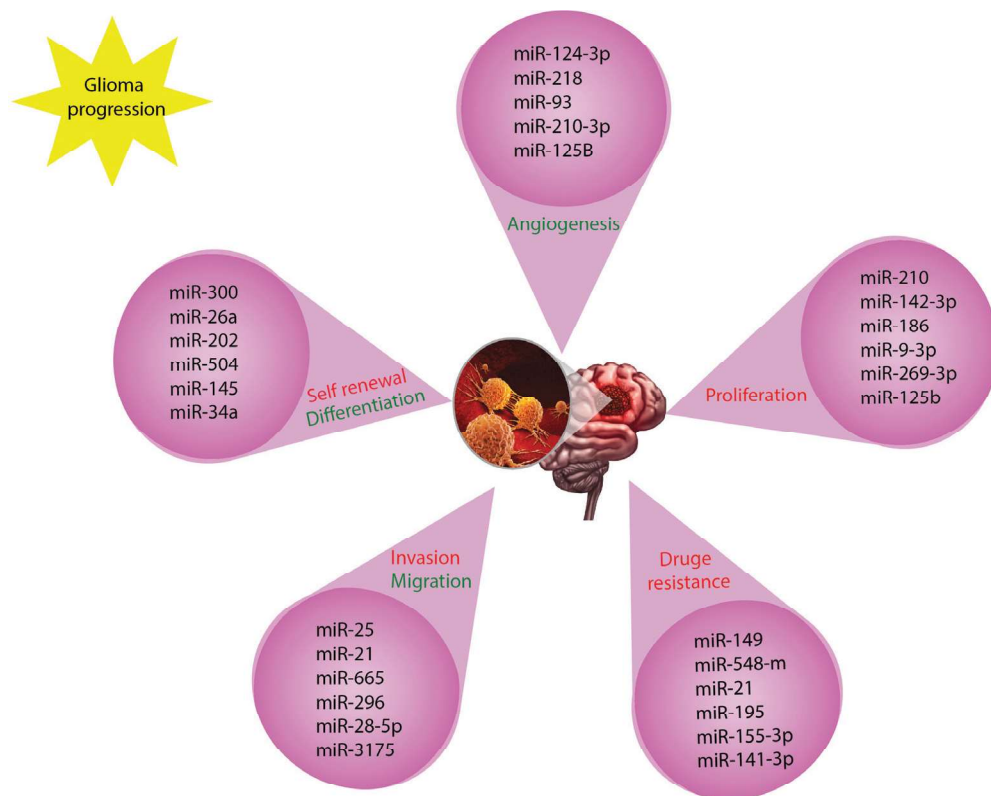


Fig. (3). Key miRNAs involved in the pathogenesis of glioblastoma. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

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- κ B, 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- κ B, 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- κ B 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- κ B 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 A β 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 A β 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 A β 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.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

The authors would like to thank Shohada Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Science, Tabriz, Iran.

REFERENCES

- [1] Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2020. *CA Cancer J. Clin.*, **2020**, *70*(1), 7-30.
<http://dx.doi.org/10.3322/caac.21590> PMID: 31912902
- [2] Zhai, K.; Siddiqui, M.; Abdellatif, B.; Liskova, A.; Kubatka, P.; Büsselberg, D. Natural compounds in glioblastoma therapy: Preclinical insights, mechanistic pathways, and outlook. *Cancers*, **2021**, *13*(10), 2317.
<http://dx.doi.org/10.3390/cancers13102317> PMID: 34065960
- [3] Tamimi, A.F.; Juweid, M. *Epidemiology and outcome of glioblastoma*; Exon Publications, **2017**, pp. 143-153.
<http://dx.doi.org/10.15586/codon.glioblastoma.2017.ch8>
- [4] Lah, T.T.; Novak, M.; Breznik, B. Brain malignancies: Glioblastoma and brain metastases. *Seminars in cancer biology*; Elsevier, **2020**.
<http://dx.doi.org/10.1016/j.semcancer.2019.10.010>
- [5] Ringel, F.; Pape, H.; Sabel, M.; Krex, D.; Bock, H.C.; Misch, M.; Weyerbrock, A.; Westermaier, T.; Senft, C.; Schucht, P.; Meyer, B.; Simon, M. Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. *Neuro-oncol.*, **2016**, *18*(1), 96-104.
<http://dx.doi.org/10.1093/neuonc/nov145> PMID: 26243790
- [6] Kalokhe, G.; Grimm, S.A.; Chandler, J.P.; Helenowski, I.; Rademaker, A.; Raizer, J.J. Metastatic glioblastoma: case presentations and a review of the literature. *J. Neurooncol.*, **2012**, *107*(1), 21-27.
<http://dx.doi.org/10.1007/s11060-011-0731-1> PMID: 21964740
- [7] Ghosh, S.; Kumar, V.; Mukherjee, H.; Lahiri, D.; Roy, P. Nutraceuical regulation of miRNAs involved in neurodegenerative diseases and brain cancers. *Heliyon*, **2021**, *7*(6), e07262.
<http://dx.doi.org/10.1016/j.heliyon.2021.e07262> PMID: 34195404
- [8] Demir, Y.; Ceylan, H.; Türkeş, C.; Beydemir, Ş. Molecular docking and inhibition studies of vulpinic, carnosic and usnic acids on polyol pathway enzymes. *J. Biomol. Struct. Dyn.*, **2022**, *40*(22), 12008-12021.
<http://dx.doi.org/10.1080/07391102.2021.1967195> PMID: 34424822
- [9] Yıldız, M.L.; Demir, Y.; Küfrevioğlu, Ö.I. Screening of *in vitro* and *in silico* effect of Fluorophenylthiourea compounds on glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase enzymes. *J. Mol. Recognit.*, **2022**, *35*(12), e2987.
<http://dx.doi.org/10.1002/jmr.2987> PMID: 36326002
- [10] Sulumer, A.N.; Palabıyık, E.; Avcı, B.; Uguz, H.; Demir, Y.; Serhat Özasan, M.; Aşkın, H. Protective effect of bromelain on some metabolic enzyme activities in tyloxapol-induced hyperlipidemic rats. *Biotechnol. Appl. Biochem.*, **2024**, *71*(1), 17-27.
<http://dx.doi.org/10.1002/bab.2517> PMID: 37749825
- [11] Davatgaran-Taghipour, Y.; Masoomzadeh, S.; Farzaei, M.H.; Bahramsoltani, R.; Karimi-Soureh, Z.; Rahimi, R.; Abdollahi, M. Polyphenol nanoformulations for cancer therapy: Experimental evidence and clinical perspective. *Int. J. Nanomed.*, **2017**, *12*, 2689-2702.
<http://dx.doi.org/10.2147/IJN.S131973> PMID: 28435252
- [12] Erices, J.I.; Torres, Á.; Niechi, I.; Bernalles, I.; Quezada, C. Current natural therapies in the treatment against glioblastoma. *Phytother. Res.*, **2018**, *32*(11), 2191-2201.
<http://dx.doi.org/10.1002/ptr.6170> PMID: 30109743
- [13] Singh, S.K. Identification of human brain tumour initiating cells. *nature*, **2004**, *432*(7015), 396-401.
<http://dx.doi.org/10.1038/nature03128>
- [14] Furnari, F.B.; Fenton, T.; Bachoo, R.M.; Mukasa, A.; Stommel, J.M.; Stegh, A.; Hahn, W.C.; Ligon, K.L.; Louis, D.N.; Brennan, C.; Chin, L.; DePinho, R.A.; Cavenee, W.K. Malignant astrocytic glioma: Genetics, biology, and paths to treatment. *Genes Dev.*, **2007**, *21*(21), 2683-2710.
<http://dx.doi.org/10.1101/gad.1596707> PMID: 17974913
- [15] Patel, A.P.; Tirosh, I.; Trombetta, J.J.; Shalek, A.K.; Gillespie, S.M.; Wakimoto, H.; Cahill, D.P.; Nahed, B.V.; Curry, W.T.; Martuza, R.L.; Louis, D.N.; Rozenblatt-Rosen, O.; Suvà, M.L.; Regev, A.; Bernstein, B.E. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. *Science*, **2014**, *344*(6190), 1396-1401.
<http://dx.doi.org/10.1126/science.1254257> PMID: 24925914
- [16] Hanif, F.; Muzaffar, K.; Perveen, K.; Malhi, S.M.; Simjee, Sh.U. *Glioblastoma multiforme: a review of its epidemiology and pathogenesis through clinical presentation and treatment*. Asian Pacific journal of cancer prevention. *APJCP*, **2017**, *18*(1), 3-9. PMID: 28239999
- [17] Lin, D.; Wang, M.; Chen, Y.; Gong, J.; Chen, L.; Shi, X.; Lan, F.; Chen, Z.; Xiong, T.; Sun, H.; Wan, S. Trends in intracranial glioma incidence and mortality in the United States, 1975-2018. *Front. Oncol.*, **2021**, *11*, 748061.
<http://dx.doi.org/10.3389/fonc.2021.748061> PMID: 34790574
- [18] Komori, T. The 2016 WHO classification of tumours of the central nervous system: The major points of revision. *Neurol. Med. Chir.*, **2017**, *57*(7), 301-311.
<http://dx.doi.org/10.2176/nmc.ra.2017-0010> PMID: 28592714
- [19] Wesseling, P.; Kros, J.M.; Jeuken, J.W.M. The pathological diagnosis of diffuse gliomas: Towards a smart synthesis of microscopic and molecular information in a multidisciplinary context. *Diagn. Histopathol.*, **2011**, *17*(11), 486-494.
<http://dx.doi.org/10.1016/j.mpdhp.2011.08.005>
- [20] Thakkar, J.P.; Dolecek, T.A.; Horbinski, C.; Ostrom, Q.T.; Lightner, D.D.; Barnholtz-Sloan, J.S.; Villano, J.L. Epidemiologic and molecular prognostic review of glioblastoma. *Cancer Epidemiol. Biomarkers Prev.*, **2014**, *23*(10), 1985-1996.
<http://dx.doi.org/10.1158/1055-9965.EPI-14-0275> PMID: 25053711
- [21] Ostrom, Q.T.; Gittleman, H.; Fulop, J.; Liu, M.; Blanda, R.; Kromer, C.; Wolinsky, Y.; Kruchko, C.; Barnholtz-Sloan, J.S. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. *Neuro-oncol.*, **2015**, *17*(Suppl 4)(Suppl. 4), iv1-iv62.
<http://dx.doi.org/10.1093/neuonc/nov189> PMID: 26511214
- [22] Phillips, H.S.; Kharbanda, S.; Chen, R.; Forrest, W.F.; Soriano, R.H.; Wu, T.D.; Misra, A.; Nigro, J.M.; Colman, H.; Soroceanu, L.; Williams, P.M.; Modrusan, Z.; Feuerstein, B.G.; Aldape, K. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell*, **2006**, *9*(3), 157-173.
<http://dx.doi.org/10.1016/j.ccr.2006.02.019> PMID: 16530701
- [23] Chen, J.; McKay, R.M.; Parada, L.F. Malignant glioma: lessons from genomics, mouse models, and stem cells. *Cell*, **2012**, *149*(1), 36-47.
<http://dx.doi.org/10.1016/j.cell.2012.03.009> PMID: 22464322
- [24] Alifieris, C.; Trafalis, D.T. Glioblastoma multiforme: Pathogenesis and treatment. *Pharmacol. Ther.*, **2015**, *152*, 63-82.
<http://dx.doi.org/10.1016/j.pharmthera.2015.05.005> PMID: 25944528
- [25] Haar, C.P.; Hebbbar, P.; Wallace, G.C., IV; Das, A.; Vandergrift, W.A., III; Smith, J.A.; Giglio, P.; Patel, S.J.; Ray, S.K.; Banik, N.L. Drug resistance in glioblastoma: A mini review. *Neurochem. Res.*, **2012**, *37*(6), 1192-1200.
<http://dx.doi.org/10.1007/s11064-011-0701-1> PMID: 22228201
- [26] Stupp, R.; Hegi, M.E.; Mason, W.P.; Van den Bent, M.J.; Taphoorn, M.J.B.; Janzer, R.C.; Ludwin, S.K.; Allgeier, A.; Fisher, B.; Belanger, K.; Hau, P.; Brandes, A.A.; Gijtenbeek, J.; Marosi, C.; Vecht, C.J.; Mokhtari, K.; Wesseling, P.; Villa, S.; Eisenhauer, E.; Gorlia, T.; Weller, M.; Lacombe, D.; Cairncross, J.G.; Mirimanoff, R.O. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.*, **2009**, *10*(5), 459-466.
[http://dx.doi.org/10.1016/S1470-2045\(09\)70025-7](http://dx.doi.org/10.1016/S1470-2045(09)70025-7) PMID: 19269895
- [27] Goldie, J.H. Drug resistance in cancer: A perspective. *Cancer Metastasis Rev.*, **2001**, *20*(1/2), 63-68.
<http://dx.doi.org/10.1023/A:1013164609041> PMID: 11831649

- [28] Anthiya, S.; Griveau, A.; Loussouarn, C.; Baril, P.; Garnett, M.; Issartel, J.P.; Garcion, E. MicroRNA-based drugs for brain tumors. *Trends Cancer*, **2018**, *4*(3), 222-238. <http://dx.doi.org/10.1016/j.trecan.2017.12.008> PMID: 29506672
- [29] Godlewski, J.; Ferrer-Luna, R.; Rooj, A.K.; Mineo, M.; Ricklefs, F.; Takeda, Y.S.; Nowicki, M.O.; Salińska, E.; Nakano, I.; Lee, H.; Weissleder, R.; Beroukhi, R.; Chiocci, E.A.; Bronisz, A. MicroRNA signatures and molecular subtypes of glioblastoma: The role of extracellular transfer. *Stem Cell Reports*, **2017**, *8*(6), 1497-1505. <http://dx.doi.org/10.1016/j.stemcr.2017.04.024> PMID: 28528698
- [30] Yi, J.; Li, S.; Wang, C.; Cao, N.; Qu, H.; Cheng, C.; Wang, Z.; Wang, L.; Zhou, L. Potential applications of polyphenols on main ncRNAs regulations as novel therapeutic strategy for cancer. *Biomed. Pharmacother.*, **2019**, *113*, 108703. <http://dx.doi.org/10.1016/j.biopha.2019.108703> PMID: 30870719
- [31] Lau, N.C.; Lim, L.P.; Weinstein, E.G.; Bartel, D.P. An abundant class of tiny RNAs with probable regulatory roles in *Caenorhabditis elegans*. *Science*, **2001**, *294*(5543), 858-862. <http://dx.doi.org/10.1126/science.1065062> PMID: 11679671
- [32] Denli, A.M.; Trops, B.B.J.; Plasterk, R.H.A.; Ketting, R.F.; Hannon, G.J. Processing of primary microRNAs by the Microprocessor complex. *Nature*, **2004**, *432*(7014), 231-235. <http://dx.doi.org/10.1038/nature03049> PMID: 15531879
- [33] Terry, L.J.; Shows, E.B.; Wenthe, S.R. Crossing the nuclear envelope: Hierarchical regulation of nucleocytoplasmic transport. *Science*, **2007**, *318*(5855), 1412-1416. <http://dx.doi.org/10.1126/science.1142204> PMID: 18048681
- [34] Pandima Devi, K.; Rajavel, T.; Daglia, M.; Nabavi, S.F.; Bishayee, A.; Nabavi, S.M. Targeting miRNAs by polyphenols: Novel therapeutic strategy for cancer. *Semin. Cancer Biol.*, **2017**, *46*, 146-157. <http://dx.doi.org/10.1016/j.semcancer.2017.02.001> PMID: 28185862
- [35] Li, H.; Chen, L.; Li, J.; Zhou, Q.; Huang, A.; Liu, W.; Wang, K.; Gao, L.; Qi, S.; Lu, Y. miR-519a enhances chemosensitivity and promotes autophagy in glioblastoma by targeting STAT3/Bcl2 signaling pathway. *J. Hematol. Oncol.*, **2018**, *11*(1), 70. <http://dx.doi.org/10.1186/s13045-018-0618-0> PMID: 29843746
- [36] Hou, Q.; Ruan, H.; Gilbert, J.; Wang, G.; Ma, Q.; Yao, W.D.; Man, H.Y. MicroRNA miR124 is required for the expression of homeostatic synaptic plasticity. *Nat. Commun.*, **2015**, *6*(1), 10045. <http://dx.doi.org/10.1038/ncomms10045> PMID: 26620774
- [37] Soreq, H.; Wolf, Y. NeurimmiRs: microRNAs in the neuroimmune interface. *Trends Mol. Med.*, **2011**, *17*(10), 548-555. <http://dx.doi.org/10.1016/j.molmed.2011.06.009> PMID: 21813326
- [38] Fowler, A.; Thomson, D.; Giles, K.; Maleki, S.; Mreich, E.; Wheeler, H.; Leedman, P.; Biggs, M.; Cook, R.; Little, N.; Robinson, B.; McDonald, K. miR-124a is frequently down-regulated in glioblastoma and is involved in migration and invasion. *Eur. J. Cancer*, **2011**, *47*(6), 953-963. <http://dx.doi.org/10.1016/j.ejca.2010.11.026> PMID: 21196113
- [39] Franzoni, E. miR-128 regulates neuronal migration, outgrowth and intrinsic excitability via the intellectual disability gene Phf6. *elife*, **2015**, *4*, e04263. <http://dx.doi.org/10.1016/j.foodchem.2013.04.050> PMID: 23790880
- [40] Campbell, K.; Booth, S.A. *MicroRNA in neurodegenerative drug discovery: the way forward?*; Taylor & Francis, **2015**, pp. 9-16.
- [41] Li, T.; Zhu, J.; Guo, L.; Shi, X.; Liu, Y.; Yang, X. Differential effects of polyphenols-enriched extracts from hawthorn fruit peels and flesh on cell cycle and apoptosis in human MCF-7 breast carcinoma cells. *Food Chem.*, **2013**, *141*(2), 1008-1018. <http://dx.doi.org/10.1016/j.foodchem.2013.04.050> PMID: 23790880
- [42] Calin, G.A.; Sevignani, C.; Dumitru, C.D.; Hyslop, T.; Noch, E.; Yendamuri, S.; Shimizu, M.; Rattan, S.; Bullrich, F.; Negrini, M.; Croce, C.M. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc. Natl. Acad. Sci. USA*, **2004**, *101*(9), 2999-3004. <http://dx.doi.org/10.1073/pnas.0307323101> PMID: 14973191
- [43] Ferdin, J.; Kunej, T.; Calin, G.A. Non-coding RNAs: identification of cancer-associated microRNAs by gene profiling. *Technol. Cancer Res. Treat.*, **2010**, *9*(2), 123-138. <http://dx.doi.org/10.1177/153303461000900202> PMID: 20218735
- [44] Croce, C.M. Causes and consequences of microRNA dysregulation in cancer. *Nat. Rev. Genet.*, **2009**, *10*(10), 704-714. <http://dx.doi.org/10.1038/nrg2634> PMID: 19763153
- [45] Aqeilan, R.I.; Calin, G.A.; Croce, C.M. miR-15a and miR-16-1 in cancer: discovery, function and future perspectives. *Cell Death Differ.*, **2010**, *17*(2), 215-220. <http://dx.doi.org/10.1038/cdd.2009.69> PMID: 19498445
- [46] Ferracin, M.; Pedriali, M.; Veronese, A.; Zagatti, B.; Gafa, R.; Magri, E.; Lunardi, M.; Munerato, G.; Querzoli, G.; Maestri, I.; Ulazzi, L.; Nenci, I.; Croce, C.M.; Lanza, G.; Querzoli, P.; Negrini, M. MicroRNA profiling for the identification of cancers with unknown primary tissue-of-origin. *J. Pathol.*, **2011**, *225*(1), 43-53. <http://dx.doi.org/10.1002/path.2915> PMID: 21630269
- [47] Mishra, P.J.; Mishra, P.J.; Banerjee, D.; Bertino, J.R. MiRSNPs or MiR-polymorphisms, new players in microRNA mediated regulation of the cell: Introducing microRNA pharmacogenomics. *Cell Cycle*, **2008**, *7*(7), 853-858. <http://dx.doi.org/10.4161/cc.7.7.5666> PMID: 18414050
- [48] Chin, L.J.; Ratner, E.; Leng, S.; Zhai, R.; Nallur, S.; Babar, I.; Muller, R.U.; Straka, E.; Su, L.; Burki, E.A.; Crowell, R.E.; Patel, R.; Kulkarni, T.; Homer, R.; Zelterman, D.; Kidd, K.K.; Zhu, Y.; Christiani, D.C.; Belinsky, S.A.; Slack, F.J.; Weidhaas, J.B. A SNP in a let-7 microRNA complementary site in the KRAS 3' untranslated region increases non-small cell lung cancer risk. *Cancer Res.*, **2008**, *68*(20), 8535-8540. <http://dx.doi.org/10.1158/0008-5472.CAN-08-2129> PMID: 18922928
- [49] Mullany, L.E.; Herrick, J.S.; Wolff, R.K.; Buas, M.F.; Slattery, M.L. Impact of polymorphisms in microRNA biogenesis genes on colon cancer risk and microRNA expression levels: a population-based, case-control study. *BMC Med. Genom.*, **2016**, *9*(1), 21. <http://dx.doi.org/10.1186/s12920-016-0181-x> PMID: 27107574
- [50] Lee, R.C.; Feinbaum, R.L.; Ambros, V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell*, **1993**, *75*(5), 843-854. [http://dx.doi.org/10.1016/0092-8674\(93\)90529-Y](http://dx.doi.org/10.1016/0092-8674(93)90529-Y) PMID: 8252621
- [51] Kawahara, Y.; Megraw, M.; Kreider, E.; Iizasa, H.; Valente, L.; Hatzigeorgiou, A.G.; Nishikura, K. Frequency and fate of microRNA editing in human brain. *Nucleic Acids Res.*, **2008**, *36*(16), 5270-5280. <http://dx.doi.org/10.1093/nar/gkn479> PMID: 18684997
- [52] Yang, W.; Chendrimada, T.P.; Wang, Q.; Higuchi, M.; Seeburg, P.H.; Shiekhattar, R.; Nishikura, K. Modulation of microRNA processing and expression through RNA editing by ADAR deaminases. *Nat. Struct. Mol. Biol.*, **2006**, *13*(1), 13-21. <http://dx.doi.org/10.1038/nsmb1041> PMID: 16369484
- [53] Galeano, F.; Tomaselli, S.; Locatelli, F.; Gallo, A. A-to-I RNA editing: The "ADAR" side of human cancer. *Semin. Cell Dev. Biol.*, **2012**, *23*(3), 244-250. <http://dx.doi.org/10.1016/j.semcdb.2011.09.003> PMID: 21930228
- [54] Choudhury, Y.; Tay, F.C.; Lam, D.H.; Sandanaraj, E.; Tang, C.; Ang, B.T.; Wang, S. Attenuated adenosine-to-inosine editing of microRNA-376a* promotes invasiveness of glioblastoma cells. *J. Clin. Invest.*, **2012**, *122*(11), 4059-4076. <http://dx.doi.org/10.1172/JCI62925> PMID: 23093778
- [55] Yang, J.S.; Phillips, M.D.; Betel, D.; Mu, P.; Ventura, A.; Siepel, A.C.; Chen, K.C.; Lai, E.C. Widespread regulatory activity of vertebrate microRNA* species. *RNA*, **2011**, *17*(2), 312-326. <http://dx.doi.org/10.1261/rna.2537911> PMID: 21177881
- [56] Chen, L.; Chen, X.R.; Zhang, R.; Li, P.; Liu, Y.; Yan, K.; Jiang, X.D. MicroRNA-107 inhibits glioma cell migration and invasion by modulating Notch2 expression. *J. Neurooncol.*, **2013**, *112*(1), 59-66. <http://dx.doi.org/10.1007/s11060-012-1037-7> PMID: 23299462
- [57] Majidinia, M.; Alizadeh, E.; Yousefi, B.; Akbarzadeh, M.; Mihanfar, A.; Rahmati-Yamchi, M.; Zarghami, N. Co-inhibition of notch and nf- κ b signaling pathway decreases proliferation through downregulating ikb- α and hes-1 expression in human ovarian cancer OVCAR-3 cells. *Drug Res.*, **2017**, *67*(1), 13-19. PMID: 27684192
- [58] Loftus, J.C.; Ross, J.T.D.; Paquette, K.M.; Paulino, V.M.; Nasser, S.; Yang, Z.; Kloss, J.; Kim, S.; Berens, M.E.; Tran, N.L. miRNA expression profiling in migrating glioblastoma cells: Regulation of cell migration and invasion by miR-23b via targeting of Pyk2. *PLoS One*, **2012**, *7*(6), e39818. <http://dx.doi.org/10.1371/journal.pone.0039818> PMID: 22745829

- [59] Møller, H.G.; Rasmussen, A.P.; Andersen, H.H.; Johnsen, K.B.; Henriksen, M.; Duroux, M. A systematic review of microRNA in glioblastoma multiforme: Micro-modulators in the mesenchymal mode of migration and invasion. *Mol. Neurobiol.*, **2013**, *47*(1), 131-144.
http://dx.doi.org/10.1007/s12035-012-8349-7 PMID: 23054677
- [60] Malzkorn, B.; Wolter, M.; Liesenberg, F.; Grzendowski, M.; Stühler, K.; Meyer, H.E.; Reifenberger, G. Identification and functional characterization of microRNAs involved in the malignant progression of gliomas. *Brain Pathol.*, **2010**, *20*(3), 539-550.
http://dx.doi.org/10.1111/j.1750-3639.2009.00328.x PMID: 19775293
- [61] Sun, G.; Cao, Y.; Shi, L.; Sun, L.; Wang, Y.; Chen, C.; Wan, Z.; Fu, L.; You, Y. Overexpressed miRNA-137 inhibits human glioma cells growth by targeting Rac1. *Cancer Biother. Radiopharm.*, **2013**, *28*(4), 327-334.
http://dx.doi.org/10.1089/cbr.2012.1380 PMID: 25310349
- [62] Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: the next generation. *Cell*, **2011**, *144*(5), 646-674.
http://dx.doi.org/10.1016/j.cell.2011.02.013 PMID: 21376230
- [63] Han, X.; Wang, J.; Sun, Y. Circulating Tumor DNA as biomarkers for cancer detection. *Genom. Proteom. Bioinforma.*, **2017**, *15*(2), 59-72.
http://dx.doi.org/10.1016/j.gpb.2016.12.004 PMID: 28392479
- [64] Ellingson, B.M.; Chung, C.; Pope, W.B.; Boxerman, J.L.; Kaufmann, T.J. Pseudoprogession, radionecrosis, inflammation or true tumor progression? challenges associated with glioblastoma response assessment in an evolving therapeutic landscape. *J. Neurooncol.*, **2017**, *134*(3), 495-504.
http://dx.doi.org/10.1007/s11060-017-2375-2 PMID: 28382534
- [65] Boisselier, B.; Gállego Pérez-Larraya, J.; Rossetto, M.; Labussière, M.; Ciccarino, P.; Marie, Y.; Delattre, J.Y.; Sanson, M. Detection of *IDH1* mutation in the plasma of patients with glioma. *Neurology*, **2012**, *79*(16), 1693-1698.
http://dx.doi.org/10.1212/WNL.0b013e31826e9b0a PMID: 23035067
- [66] Capper, D.; Simon, M.; Langhans, C.D.; Okun, J.G.; Tonn, J.C.; Weller, M.; Deimling, A.; Hartmann, C. 2-Hydroxyglutarate concentration in serum from patients with gliomas does not correlate with IDH1/2 mutation status or tumor size. *Int. J. Cancer*, **2012**, *131*(3), 766-768.
http://dx.doi.org/10.1002/ijc.26425 PMID: 21913188
- [67] Contreras-Naranjo, J.C.; Wu, H.J.; Ugaz, V.M. Microfluidics for exosome isolation and analysis: Enabling liquid biopsy for personalized medicine. *Lab Chip*, **2017**, *17*(21), 3558-3577.
http://dx.doi.org/10.1039/C7LC00592J PMID: 28832692
- [68] Kucharzewska, P.; Belting, M. Emerging roles of extracellular vesicles in the adaptive response of tumour cells to microenvironmental stress. *J. Extracell. Vesicles*, **2013**, *2*(1), 20304.
http://dx.doi.org/10.3402/jev.v2i0.20304 PMID: 24009895
- [69] Morishita, M.; Takahashi, Y.; Nishikawa, M.; Sano, K.; Kato, K.; Yamashita, T.; Imai, T.; Saji, H.; Takakura, Y. Quantitative analysis of tissue distribution of the B16BL6-derived exosomes using a streptavidin-lactadherin fusion protein and iodine-125-labeled biotin derivative after intravenous injection in mice. *J. Pharm. Sci.*, **2015**, *104*(2), 705-713.
http://dx.doi.org/10.1002/jps.24251 PMID: 25393546
- [70] Shao, H.; Chung, J.; Lee, K.; Balaj, L.; Min, C.; Carter, B.S.; Hochberg, F.H.; Breakefield, X.O.; Lee, H.; Weissleder, R. Chip-based analysis of exosomal mRNA mediating drug resistance in glioblastoma. *Nat. Commun.*, **2015**, *6*(1), 6999.
http://dx.doi.org/10.1038/ncomms7999 PMID: 25959588
- [71] Muller, L.; Muller-Haegeler, S.; Mitsuhashi, M.; Gooding, W.; Okada, H.; Whiteside, T.L. Exosomes isolated from plasma of glioma patients enrolled in a vaccination trial reflect antitumor immune activity and might predict survival. *OncolImmunology*, **2015**, *4*(6), e1008347.
http://dx.doi.org/10.1080/2162402X.2015.1008347 PMID: 26155415
- [72] Regazzo, G.; Terrenato, I.; Spagnuolo, M.; Carosi, M.; Cognetti, G.; Cicchillitti, L.; Sperati, F.; Villani, V.; Carapella, C.; Piaggio, G.; Pelosi, A.; Rizzo, M.G. A restricted signature of serum miRNAs distinguishes glioblastoma from lower grade gliomas. *J. Exp. Clin. Cancer Res.*, **2016**, *35*(1), 124.
http://dx.doi.org/10.1186/s13046-016-0393-0 PMID: 27476114
- [73] Wang, Q.; Li, P.; Li, A.; Jiang, W.; Wang, H.; Wang, J.; Xie, K. Plasma specific miRNAs as predictive biomarkers for diagnosis and prognosis of glioma. *J. Exp. Clin. Cancer Res.*, **2012**, *31*(1), 97.
http://dx.doi.org/10.1186/1756-9966-31-97 PMID: 23174013
- [74] Zhao, H.; Shen, J.; Hodges, T.R.; Song, R.; Fuller, G.N.; Heimberger, A.B. Serum microRNA profiling in patients with glioblastoma: A survival analysis. *Mol. Cancer*, **2017**, *16*(1), 59.
http://dx.doi.org/10.1186/s12943-017-0628-5 PMID: 28284220
- [75] Piwecka, M.; Rolke, K.; Belter, A.; Barciszewska, A.M.; Żywicki, M.; Michalak, M.; Nowak, S.; Naskręt-Barciszewska, M.Z.; Barciszewski, J. Comprehensive analysis of microRNA expression profile in malignant glioma tissues. *Mol. Oncol.*, **2015**, *9*(7), 1324-1340.
http://dx.doi.org/10.1016/j.molonc.2015.03.007 PMID: 25864039
- [76] Xu, Q.; Liu, L.Z.; Qian, X.; Chen, Q.; Jiang, Y.; Li, D.; Lai, L.; Jiang, B.H. MiR-145 directly targets p70S6K1 in cancer cells to inhibit tumor growth and angiogenesis. *Nucleic Acids Res.*, **2012**, *40*(2), 761-774.
http://dx.doi.org/10.1093/nar/gkr730 PMID: 21917858
- [77] Wei, J.; Nduom, E.K.; Kong, L.Y.; Hashimoto, Y.; Xu, S.; Gabrusiewicz, K.; Ling, X.; Huang, N.; Qiao, W.; Zhou, S.; Ivan, C.; Fuller, G.N.; Gilbert, M.R.; Overwijk, W.; Calin, G.A.; Heimberger, A.B. MiR-138 exerts anti-glioma efficacy by targeting immune checkpoints. *Neuro-oncol.*, **2016**, *18*(5), 639-648.
http://dx.doi.org/10.1093/neuonc/nov292 PMID: 26658052
- [78] Alvarado, A.G.; Turaga, S.M.; Sathyan, P.; Mulkearns-Hubert, E.E.; Otvos, B.; Silver, D.J.; Hale, J.S.; Flavahan, W.A.; Zimm, P.O.; Sinyuk, M.; Li, M.; Guda, M.R.; Velpula, K.K.; Tsung, A.J.; Nakano, I.; Vogelbaum, M.A.; Majumder, S.; Rich, J.N.; Lathia, J.D. Coordination of self-renewal in glioblastoma by integration of adhesion and microRNA signaling. *Neuro-oncol.*, **2016**, *18*(5), 656-666.
http://dx.doi.org/10.1093/neuonc/nov196 PMID: 26374689
- [79] El Fatimy, R.; Subramanian, S.; Uhlmann, E.J.; Krichevsky, A.M. Genome editing reveals glioblastoma addiction to microRNA-10b. *Mol. Ther.*, **2017**, *25*(2), 368-378.
http://dx.doi.org/10.1016/j.ymthe.2016.11.004 PMID: 28153089
- [80] Fareh, M.; Almairac, F.; Turchi, L.; Burel-Vandenbos, F.; Paquis, P.; Fontaine, D.; Lacas-Gervais, S.; Junier, M.P.; Chneiweiss, H.; Virolle, T. Cell-based therapy using miR-302-367 expressing cells represses glioblastoma growth. *Cell Death Dis.*, **2017**, *8*(3), e2713-e2713.
http://dx.doi.org/10.1038/cddis.2017.117 PMID: 28358371
- [81] Wang, Y.; Jiang, F.; Xiong, Y.; Cheng, X.; Qiu, Z.; Song, R. LncRNA TTN-AS1 sponges miR-376a-3p to promote colorectal cancer progression via upregulating KLF15. *Life Sci.*, **2020**, *244*, 116936.
http://dx.doi.org/10.1016/j.lfs.2019.116936 PMID: 31610194
- [82] Cheng, Z.; Zou, X.; Jin, Y.; Gao, S.; Lv, J.; Li, B.; Cui, R. The Role of KLF₄ in Alzheimer's Disease. *Front. Cell. Neurosci.*, **2018**, *12*, 325.
http://dx.doi.org/10.3389/fncel.2018.00325 PMID: 30297986
- [83] Chen, Y.; Peng, S.; Cen, H.; Lin, Y.; Huang, C.; Chen, Y.; Shan, H.; Su, Y.; Zeng, L. MicroRNA hsa-miR-623 directly suppresses MMP1 and attenuates IL-8-induced metastasis in pancreatic cancer. *Int. J. Oncol.*, **2019**, *55*(1), 142-156.
http://dx.doi.org/10.3892/ijo.2019.4803 PMID: 31115512
- [84] Luo, H.; Xu, R.; Chen, B.; Dong, S.; Zhou, F.; Yu, T.; Xu, G.; Zhang, J.; Wang, Y.; You, Y. MicroRNA-940 inhibits glioma cells proliferation and cell cycle progression by targeting CKS1. *Am. J. Transl. Res.*, **2019**, *11*(8), 4851-4865.
PMID: 31497204
- [85] Wang, J.; Chen, C.; Yan, X.; Wang, P. The role of miR-382-5p in glioma cell proliferation, migration and invasion. *OncoTargets Ther.*, **2019**, *12*, 4993-5002.
http://dx.doi.org/10.2147/OTT.S196322 PMID: 31417288
- [86] Zhou, X.; Yang, Y.; Ma, P.; Wang, N.; Yang, D.; Tu, Q.; Sun, B.; Xiang, T.; Zhao, X.; Hou, Z.; Fang, X. TRIM44 is indispensable for glioma cell proliferation and cell cycle progression through AKT/p21/p27 signaling pathway. *J. Neurooncol.*, **2019**, *145*(2), 211-222.

- <http://dx.doi.org/10.1007/s11060-019-03301-0> PMID: 31605296
- [87] Cui, D.; Wang, K.; Liu, Y.; Gao, J.; Cui, J. MicroRNA-623 Inhibits Epithelial-Mesenchymal Transition to Attenuate Glioma Proliferation by Targeting TRIM44. *OncoTargets Ther.*, **2020**, *13*, 9291-9303.
- [88] <http://dx.doi.org/10.2147/OTT.S250497> PMID: 33061418
- Jordan, M.L.; Delunas, L.R. Quality of life and patterns of nontraditional therapy use by patients with cancer. in *Oncology Nursing Forum.*, **2001**.
- [89] Peacock, O.; Lee, A.C.; Cameron, F.; Tarbox, R.; Vafadar-Isfahani, N.; Tufarelli, C.; Lund, J.N. Inflammation and MiR-21 pathways functionally interact to downregulate PDCD4 in colorectal cancer. *PLoS One*, **2014**, *9*(10), e110267.
- [90] <http://dx.doi.org/10.1371/journal.pone.0110267> PMID: 25310697
- Jiao, W.; Leng, X.; Zhou, Q.; Wu, Y.; Sun, L.; Tan, Y.; Ni, H.; Dong, X.; Shen, T.; Liu, Y.; Li, J. Different miR-21-3p isoforms and their different features in colorectal cancer. *Int. J. Cancer*, **2017**, *141*(10), 2103-2111.
- [91] <http://dx.doi.org/10.1002/ijc.30902> PMID: 28734015
- Diosdado, B.; van de Wiel, M.A.; Terhaar Sive Droste, J.S.; Mongera, S.; Postma, C.; Meijerink, W.J.H.J.; Carvalho, B.; Meijer, G.A. MiR-17-92 cluster is associated with 13q gain and c-myc expression during colorectal adenoma to adenocarcinoma progression. *Br. J. Cancer*, **2009**, *101*(4), 707-714.
- [92] <http://dx.doi.org/10.1038/sj.bjc.6605037> PMID: 19672269
- Dews, M.; Homayouni, A.; Yu, D.; Murphy, D.; Sevignani, C.; Wentzel, E.; Furth, E.E.; Lee, W.M.; Enders, G.H.; Mendell, J.T.; Thomas-Tikhonenko, A. Augmentation of tumor angiogenesis by a Myc-activated microRNA cluster. *Nat. Genet.*, **2006**, *38*(9), 1060-1065.
- [93] <http://dx.doi.org/10.1038/ng1855> PMID: 16878133
- Botti, G.; Marra, L.; Malzone, M.; Anniciello, A.; Botti, C.; Franco, R.; Cantile, M. LncRNA HOTAIR as prognostic circulating marker and potential therapeutic target in patients with tumor diseases. *Curr. Drug Targets*, **2016**, *18*(1), 27-34.
- [94] <http://dx.doi.org/10.2174/1389450117666151209122950> PMID: 26648066
- Yousefi, B. Peroxisome proliferator-activated receptors and their ligands in cancer drug-resistance: Opportunity or challenge. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, **2016**, *16*(12), 1541-1545.
- [95] <http://dx.doi.org/10.2174/1871520616666160204112941>
- Yousefi, B.; Samadi, N.; Baradaran, B.; Rameshknia, V.; Shafiei-Irannejad, V.; Majidinia, M.; Targhaze, N.; Zarghami, N. Differential effects of peroxisome proliferator-activated receptor agonists on doxorubicin-resistant human myelogenous leukemia (K562/DOX) cells. *Cell. Mol. Biol.*, **2015**, *61*(8), 118-122. PMID: 26718439
- [96] Ahmadi, D.; Zarei, M.; Rahimi, M.; Khazaie, M.; Asemi, Z.; Mir, S.M.; Sadeghpour, A.; Karimian, A.; Alemi, F.; Rahmati-Yamchi, M.; Salehi, R.; Jadidi-Niaragh, F.; Yousefi, M.; Khelgati, N.; Majidinia, M.; Safa, A.; Yousefi, B. Preparation and *in-vitro* evaluation of pH-responsive cationic cyclodextrin coated magnetic nanoparticles for delivery of methotrexate to the Saos-2 bone cancer cells. *J. Drug Deliv. Sci. Technol.*, **2020**, *57*, 101584.
- [97] <http://dx.doi.org/10.1016/j.jddst.2020.101584>
- Guan, Y.; Li, M.; Qiu, Z.; Xu, J.; Zhang, Y.; Hu, N.; Zhang, X.; Guo, W.; Yuan, J.; Shi, Q.; Wang, W. Comprehensive analysis of DOK family genes expression, immune characteristics, and drug sensitivity in human tumors. *J. Adv. Res.*, **2022**, *36*, 73-87.
- [98] <http://dx.doi.org/10.1016/j.jare.2021.06.008> PMID: 35127166
- Yallapu, M.M.; Jaggi, M.; Chauhan, S.C. Curcumin nanoformulations: A future nanomedicine for cancer. *Drug Discov. Today*, **2012**, *17*(1-2), 71-80.
- [99] <http://dx.doi.org/10.1016/j.drudis.2011.09.009> PMID: 21959306
- Shi, X.; Valizadeh, A.; Mir, S.M.; Asemi, Z.; Karimian, A.; Majidinia, M.; Safa, A.; Yosefi, B. miRNA-29a reverses P-glycoprotein-mediated drug resistance and inhibits proliferation via up-regulation of PTEN in colon cancer cells. *Eur. J. Pharmacol.*, **2020**, *880*, 173138.
- [100] <http://dx.doi.org/10.1016/j.ejphar.2020.173138> PMID: 32416187
- Schexnayder, C.; Stratford, R. Genistein and glyceollin effects on ABC2 (MRP2) and ABCG2 (BCRP) in Caco-2 cells. *Int. J. Environ. Res. Public Health*, **2015**, *13*(1), 17.
- [101] <http://dx.doi.org/10.3390/ijerph13010017> PMID: 26703673
- Desai, V.; Bhushan, A. Natural bioactive compounds: Alternative approach to the treatment of glioblastoma multiforme. *BioMed res. Int.*, **2017**.
- [102] <http://dx.doi.org/10.1155/2017/9363040>
- Loria, R.; Bon, G.; Perotti, V.; Gallo, E.; Bersani, I.; Baldassari, P.; Porru, M.; Leonetti, C.; Di Carlo, S.; Visca, P.; Brizzi, M.F.; Anichini, A.; Mortarini, R.; Falcioni, R. Sema6A and Mical1 control cell growth and survival of BRAFV600E human melanoma cells. *Oncotarget*, **2015**, *6*(5), 2779-2793.
- [103] <http://dx.doi.org/10.18632/oncotarget.2995> PMID: 25576923
- Kim, S.J.; Hwang, E.; Yi, S.S.; Song, K.D.; Lee, H.K.; Heo, T.H.; Park, S.K.; Jung, Y.J.; Jun, H.S. Sea buckthorn leaf extract inhibits glioma cell growth by reducing reactive oxygen species and promoting apoptosis. *Appl. Biochem. Biotechnol.*, **2017**, *182*(4), 1663-1674.
- [104] <http://dx.doi.org/10.1007/s12010-017-2425-4> PMID: 28181191
- Statello, L.; Guo, C.J.; Chen, L.L.; Huarte, M. Gene regulation by long non-coding RNAs and its biological functions. *Nat. Rev. Mol. Cell Biol.*, **2021**, *22*(2), 96-118.
- [105] <http://dx.doi.org/10.1038/s41580-020-00315-9> PMID: 33353982
- Goenka, A.; Ganesh, S. Role of long non-coding RNAs in cellular stress response. *Proc. Indian Natl. Sci. Acad.*, **2018**.
- [106] Peng, Z.; Liu, C.; Wu, M. New insights into long noncoding RNAs and their roles in glioma. *Mol. Cancer*, **2018**, *17*(1), 61.
- [107] <http://dx.doi.org/10.1186/s12943-018-0812-2> PMID: 29458374
- Balas, M.M.; Johnson, A.M. Exploring the mechanisms behind long noncoding RNAs and cancer. *Noncoding RNA Res.*, **2018**, *3*(3), 108-117.
- [108] <http://dx.doi.org/10.1016/j.ncrna.2018.03.001> PMID: 30175284
- Slack, F.J.; Chinnaiyan, A.M. The role of non-coding RNAs in oncology. *Cell*, **2019**, *179*(5), 1033-1055.
- [109] <http://dx.doi.org/10.1016/j.cell.2019.10.017> PMID: 31730848
- Jain, A.K.; Xi, Y.; McCarthy, R.; Allton, K.; Akdemir, K.C.; Patel, L.R.; Aronow, B.; Lin, C.; Li, W.; Yang, L.; Barton, M.C. LncPRESS1 is a p53-regulated LncRNA that safeguards pluripotency by disrupting SIRT6-mediated de-acetylation of histone H3K56. *Mol. Cell*, **2016**, *64*(5), 967-981.
- [110] <http://dx.doi.org/10.1016/j.molcel.2016.10.039> PMID: 27912097
- Lin, A.; Li, C.; Xing, Z.; Hu, Q.; Liang, K.; Han, L.; Wang, C.; Hawke, D.H.; Wang, S.; Zhang, Y.; Wei, Y.; Ma, G.; Park, P.K.; Zhou, J.; Zhou, Y.; Hu, Z.; Zhou, Y.; Marks, J.R.; Liang, H.; Hung, M.C.; Lin, C.; Yang, L. The LINK-A lncRNA activates normoxic HIF1 α signalling in triple-negative breast cancer. *Nat. Cell Biol.*, **2016**, *18*(2), 213-224.
- [111] <http://dx.doi.org/10.1038/ncb3295> PMID: 26751287
- Stackhouse, C.T.; Gillespie, G.Y.; Willey, C.D. Exploring the roles of lncRNAs in GBM pathophysiology and their therapeutic potential. *Cells*, **2020**, *9*(11), 2369.
- [112] <http://dx.doi.org/10.3390/cells9112369> PMID: 33126510
- Desai, V.; Bhushan, A. Natural Bioactive Compounds: Alternative approach to the treatment of glioblastoma multiforme. *BioMed Res. Int.*, **2017**, *2017*, 1-10.
- [113] <http://dx.doi.org/10.1155/2017/9363040> PMID: 29359162
- Vengoji, R.; Bhushan, A. Natural products: A hope for glioblastoma patients. *Oncotarget*, **2018**, *9*(31), 22194-22219.
- [114] Chen, T.; da Fonseca, C.; Schöenthal, A. Intranasal perillyl alcohol for glioma therapy: Molecular mechanisms and clinical development. *Int. J. Mol. Sci.*, **2018**, *19*(12), 3905.
- [115] <http://dx.doi.org/10.3390/ijms19123905> PMID: 30563210
- Bryukhovetskiy, I.; Lyakhova, I.; Mischenko, P.; Milkina, E.; Zaitsev, S.; Khotimchenko, Y.; Bryukhovetskiy, A.; Polevshchikov, A.; Kudryavtsev, I.; Khotimchenko, M.; Zhidkov, M. Alkaloids of fascaplysin are effective conventional chemotherapeutic drugs, inhibiting the proliferation of C6 glioma cells and causing their death *in vitro*. *Oncol. Lett.*, **2017**, *13*(2), 738-746.
- [116] <http://dx.doi.org/10.3892/ol.2016.5478> PMID: 28356953
- Bangaru, M.L.; Chen, S.; Woodliff, J.; Kansra, S. Curcumin (diferuloylmethane) induces apoptosis and blocks migration of human medulloblastoma cells. *Anticancer Res.*, **2010**, *30*(2), 499-504.
- [117] PMID: 20332461
- Wang, K.; Fu, X.; Li, Y.; Hou, Y.; Yang, M.; Sun, J.; Yi, S.; Fan, C.; Fu, X.; Zhai, J.; Sun, B. Induction of s-phase arrest in human

- glioma cells by selenocysteine, a natural selenium-containing agent via triggering reactive oxygen species-mediated dna damage and modulating mapks and akt pathways. *Neurochem. Res.*, **2016**, *41*(6), 1439-1447.
<http://dx.doi.org/10.1007/s11064-016-1854-8> PMID: 26846141
- [118] Mirzaei, H.; Fathollahzadeh, S.; Khanmohammadi, R.; Darijani, M.; Momeni, F.; Masoudifar, A.; Goodarzi, M.; Mardanshah, O.; Stenvang, J.; Jaafari, M.R.; Mirzaei, H.R. State of the art in microRNA as diagnostic and therapeutic biomarkers in chronic lymphocytic leukemia. *J. Cell. Physiol.*, **2018**, *233*(2), 888-900.
<http://dx.doi.org/10.1002/jcp.25799> PMID: 28084621
- [119] Keshavarzi, M.; Darijani, M.; Momeni, F.; Moradi, P.; Ebrahimnejad, H.; Masoudifar, A.; Mirzaei, H. Molecular imaging and oral cancer diagnosis and therapy. *J. Cell. Biochem.*, **2017**, *118*(10), 3055-3060.
<http://dx.doi.org/10.1002/jcb.26042> PMID: 28390191
- [120] Munoz, J.L.; Bliss, S.A.; Greco, S.J.; Ramkissoon, S.H.; Ligon, K.L.; Rameshwar, P. Delivery of functional anti-mir-9 by mesenchymal stem cell-derived exosomes to glioblastoma multiforme cells conferred chemosensitivity. *Mol. Ther. Nucleic Acids*, **2013**, *2*(10), e126.
<http://dx.doi.org/10.1038/mtna.2013.60> PMID: 24084846
- [121] Zhou, S.; Zhang, S.; Shen, H.; Chen, W.; Xu, H.; Chen, X.; Sun, D.; Zhong, S.; Zhao, J.; Tang, J. Curcumin inhibits cancer progression through regulating expression of microRNAs. *Tumour Biol.*, **2017**, *39*(2)
<http://dx.doi.org/10.1177/1010428317691680> PMID: 28222667
- [122] Roy, S.; Yu, Y.; Padhye, S.B.; Sarkar, F.H.; Majumdar, A.P.N. Difluorinated-curcumin (CDF) restores PTEN expression in colon cancer cells by down-regulating miR-21. *PLoS One*, **2013**, *8*(7), e68543.
<http://dx.doi.org/10.1371/journal.pone.0068543> PMID: 23894315
- [123] Golden, E.B.; Lam, P.Y.; Kardosh, A.; Gaffney, K.J.; Cadenas, E.; Louie, S.G.; Petasis, N.A.; Chen, T.C.; Schöenthal, A.H. Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors. *Blood*, **2009**, *113*(23), 5927-5937.
<http://dx.doi.org/10.1182/blood-2008-07-171389> PMID: 19190249
- [124] Chakrabarti, M.; Ai, W.; Banik, N.L.; Ray, S.K. Overexpression of miR-7-1 increases efficacy of green tea polyphenols for induction of apoptosis in human malignant neuroblastoma SH-SY5Y and SK-N-DZ cells. *Neurochem. Res.*, **2013**, *38*(2), 420-432.
<http://dx.doi.org/10.1007/s11064-012-0936-5> PMID: 23192662
- [125] Kim, H.E.; Oh, J.H.; Lee, S.K.; Oh, Y.J. Ginsenoside RH-2 induces apoptotic cell death in rat C6 glioma via a reactive oxygen and caspase-dependent but Bcl-XL-independent pathway. *Life Sci.*, **1999**, *65*(3), PL33-PL40.
[http://dx.doi.org/10.1016/S0024-3205\(99\)00252-0](http://dx.doi.org/10.1016/S0024-3205(99)00252-0) PMID: 10447219
- [126] Wu, N.; Wu, G.; Hu, R.; Li, M.; Feng, H. Ginsenoside Rh2 inhibits glioma cell proliferation by targeting microRNA-128. *Acta Pharmacol. Sin.*, **2011**, *32*(3), 345-353.
<http://dx.doi.org/10.1038/aps.2010.220> PMID: 21372826
- [127] Han, J.; Chen, Q. MiR-16 modulate temozolomide resistance by regulating BCL-2 in human glioma cells. *Int. J. Clin. Exp. Pathol.*, **2015**, *8*(10), 12698-12707.
 PMID: 26722459
- [128] Zhang, S.; Liu, X.; Sun, C.; Yang, J.; Wang, L.; Liu, J.; Gong, L.; Jing, Y. Apigenin attenuates experimental autoimmune myocarditis by modulating th1/th2 cytokine balance in mice. *Inflammation*, **2016**, *39*(2), 678-686.
<http://dx.doi.org/10.1007/s10753-015-0294-y> PMID: 26658748
- [129] Chen, X.J.; Wu, M.Y.; Li, D.H.; You, J. Apigenin inhibits glioma cell growth through promoting microRNA-16 and suppression of BCL-2 and nuclear factor- κ B/MMP-9. *Mol. Med. Rep.*, **2016**, *14*(3), 2352-2358.
<http://dx.doi.org/10.3892/mmr.2016.5460> PMID: 27430517
- [130] Dirscherl, K.; Karlstetter, M.; Ebert, S.; Kraus, D.; Hlawatsch, J.; Walczak, Y.; Moehle, C.; Fuchshofer, R.; Langmann, T. Luteolin triggers global changes in the microglial transcriptome leading to a unique anti-inflammatory and neuroprotective phenotype. *J. Neuroinflammation*, **2010**, *7*(1), 3.
<http://dx.doi.org/10.1186/1742-2094-7-3> PMID: 20074346
- [131] Albani, D.; Polito, L.; Forloni, G. Sirtuins as novel targets for Alzheimer's disease and other neurodegenerative disorders: Experimental and genetic evidence. *J. Alzheimers Dis.*, **2010**, *19*(1), 11-26.
<http://dx.doi.org/10.3233/JAD-2010-1215> PMID: 20061622
- [132] Saiko, P.; Szakmary, A.; Jaeger, W.; Szekeres, T. Resveratrol and its analogs: Defense against cancer, coronary disease and neurodegenerative maladies or just a fad? *Mutat. Res. Rev. Mutat. Res.*, **2008**, *658*(1-2), 68-94.
<http://dx.doi.org/10.1016/j.mrrev.2007.08.004> PMID: 17890139
- [133] Kiskova, T.; Kubatka, P.; Büßelberg, D.; Kassayova, M. The plant-derived compound resveratrol in brain cancer: A review. *Biomolecules*, **2020**, *10*(1), 161.
<http://dx.doi.org/10.3390/biom10010161> PMID: 31963897
- [134] Chan, J.A.; Krichevsky, A.M.; Kosik, K.S. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. *Cancer Res.*, **2005**, *65*(14), 6029-6033.
<http://dx.doi.org/10.1158/0008-5472.CAN-05-0137> PMID: 16024602
- [135] Corsten, M.F.; Miranda, R.; Kasmieh, R.; Krichevsky, A.M.; Weissleder, R.; Shah, K. MicroRNA-21 knockdown disrupts glioma growth *in vivo* and displays synergistic cytotoxicity with neural precursor cell delivered S-TRAIL in human gliomas. *Cancer Res.*, **2007**, *67*(19), 8994-9000.
<http://dx.doi.org/10.1158/0008-5472.CAN-07-1045> PMID: 17908999
- [136] Li, H.; Jia, Z.; Li, A.; Jenkins, G.; Yang, X.; Hu, J.; Guo, W. Resveratrol repressed viability of U251 cells by miR-21 inhibiting of NF- κ B pathway. *Mol. Cell. Biochem.*, **2013**, *382*(1-2), 137-143.
<http://dx.doi.org/10.1007/s11010-013-1728-1> PMID: 23793554