Neurochemistry International 150 (2021) 105168

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Safety and Efficacy Assessments to Take Antioxidants in Glioblastoma Therapy: From *In Vitro* Experiences to Animal and Clinical Studies

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ARTICLE INFO

Keywords:
Glioblastoma
Antioxidants
Clinical trials
Anti-glioblastoma therapy
Dietary supplements

ABSTRACT

Glioblastoma (GBM) is considered one of the most common malignant brain tumors, occurring as over 15% of all primary central nervous system and brain neoplasms. The unique and standard treatment option towards GBM involves the combination of surgical resection followed by radiotherapy (RT) and chemotherapy (CT). However, due to the aggressive nature and heterogeneity of GBMs, they remained difficult to treat. Recent findings from preclinical studies have revealed that disruption of the redox balance via using either oxidative or anti-oxidative agents in GBM presented an effective and promising therapeutic approach. A limited number of clinical trials substantially encouraged their concomitant use with RT or CT. Thus, treatment of GBMs may benefit from natural or synthetic antioxidative compounds as novel therapeutics. Despite the presence of variegated *in vitro* and *in vivo* studies focusing on safety and efficacy issues of these promising therapeutics, nowadays their translation to clinics is far from applicability due to several challenges. In this review, we briefly introduce the enzymatic and non-enzymatic antioxidant defense systems as well as potential signaling pathways related to the pathogenesis of GBM with a special interest in antioxidant mechanisms. In addition, we describe the advantages and limitations of antioxidant supplementation in GBM cases or disease models as well as growing challenges for GBM therapies with antioxidants in the future.

1. Introduction

Glioblastoma (GBM) is one of the most common malignant brain tumors that can constitute over 15% of all primary central nervous system and brain neoplasms (Thakkar et al., 2014). GBM has a 3.2/100, 000 incidence rate adjusted for average age that most common disease occurrence (Ostrom et al., 2019). Although GBM usually occurs in the brain, it can also be seen in the spinal cord, cerebellum and brainstem. GBMs were known to be originated primarily from glial cells. However, GBMs can be derived from a various number of cell types that show stem cell-like features (Blissitt, 2014). These types of cells are at a different phase of the differentiation that produces glial or neuronal cells and phenotypic differentiations are determined by signaling pathway modifications instead of cell type origins (Phillips et al., 2006). Although GBM is a common disease for 64-year-olds on average, it can be seen in people of all ages, including children and is more common in men than women (Ellor et al., 2014). When GBMs occur without a known origin or precursors, are classified as primary tumors but there are also secondary GBM that originate from lower grade tumors, differentiating into GBM. Generally, GBMs emerge as primary tumors and these types of GBMs present difficulty in prognosis, and are commonly seen in older patients (Wilson et al., 2014).

According to the Cancer Genome Atlas project, 200 human tumor samples were analyzed and nearly 600 associated genes were identified (Parsons et al., 2008). This project uncovered the complex genetic profile of GBM and revealed commonly activated sets of signaling pathways related to GBM. These pathways were shown to commonly include the retinoblastoma pathway, the receptor tyrosine kinase/R-as/phosphoinositide 3-kinase signaling pathway and the tumor protein p53 pathway. Moreover, these pathways were shown to have crucial properties for cell proliferation and survival. Pathway alteration was investigated to reveal GBM's survival properties like cell-cycle

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https://doi.org/10.1016/j.neuint.2021.105168
Received 23 March 2021; Received in revised form 16 August 2021; Accepted 17 August 2021
Available online 25 August 2021

checkpoint, apoptosis and senescence escape mechanisms (Chen et al., 2012). Also, the different genetic alterations were shown to result in an either primary or secondary glioma. For instance, a mutation in phosphate and tensin homolog (PTEN) or overexpression of epidermal growth factor receptor (EGFR) results in primary GBMs, while mutation in P53 or isocitrate dehydrogenase 1 (IDH1) produce secondary GBMs (Chen et al., 2012; Young et al., 2015).

GBM progression is closely related to tissue microenvironment and gliomagenesis. A pro-inflammatory microenvironment that leads to changes in redox homeostasis promotes gliomagenesis (Feng et al., 2015). Therefore, some alternative therapies have focused on the development of new approaches that can regulate the redox state in the glioblastoma microenvironment or stimulate ROS production (Manda et al., 2015). The main aim of this review is to procure convenient data about the anti-GBM effects of natural or synthetic antioxidants on different signaling pathways in the carcinogenesis of GBM. Here we assess the potential benefits or limitations of antioxidant use towards the prevention and treatment of GBM. We generated the data from biomedical literature by use of antioxidant, glioblastoma, *in vitro*, animal model, clinical trial as keywords for scanning in the PubMed database. We have searched noteworthy scientific articles or reviews from the years 1979–2021 to create this study.

2. Antioxidant defense systems

The antioxidant defense system comprises different functional groups that can be classified into three lines of defense. The first defense, preventive antioxidants, function in preventing the formation of new free radicals. The antioxidants in this group are enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX); proteins that bind metals such as ferritin and ceruloplasmin; and minerals such as Se, Cu, and Zn. The antioxidants in second-line defense scavenge different free radicals. Glutathione, albumin, vitamins C and E, carotenoids, and flavonoids are radical scavenging antioxidants. Third line antioxidants including lipases, proteases, DNA repair enzymes, transferases, and methionine-sulfoxide reductases are responsible for repairing the damage in biomolecules induced by free radicals (Fig. 1) (Irshad and Chaudhuri, 2002; Ramírez-Expósito and Martínez-Martos, 2019; Shetti et al., 2009; Sindhi et al., 2013).

The imbalance between the level of free radicals and antioxidant systems leads to oxidative stress. Disruption of the balance between ROS and antioxidant levels can rearrange defense mechanisms in cells, promoting excessive cell proliferation and tumorigenesis. Antioxidant defense systems prevent oxidative stress by detoxifying the deleterious effects of ROS. Therefore, it is thought that they may be beneficial in disorders associated with oxidative stress. Mammalian cells have been protected by developing various antioxidant mechanisms to resist the harmful actions of ROS and cellular oxidative stress (Aoyama et al., 2008). Antioxidants consist of different types of molecular groups. Several endogenous metabolites, water or lipid-soluble low molecular weight substances and enzymes such as SOD, CAT, GR and GPx have antioxidant functions in the cell (Fig. 2).

2.1. Non-enzymatic antioxidant defense system

Glutathione (GSH) is the most abundant low molecular weight thiol and plays a role in keeping the balance of cellular redox state (Chuang et al., 2003; Guha et al., 2011). Glutathione primarily exists in reduced form as GSH in the cell. However, some is present as GSSG in the form of oxidized disulfide. The level of oxidized form (glutathione disulfide, GSSG) is increased by oxidative stress, resulting in harmful effects in the cellular system (Salazar-Ramiro et al., 2016). Therefore, low GSH level

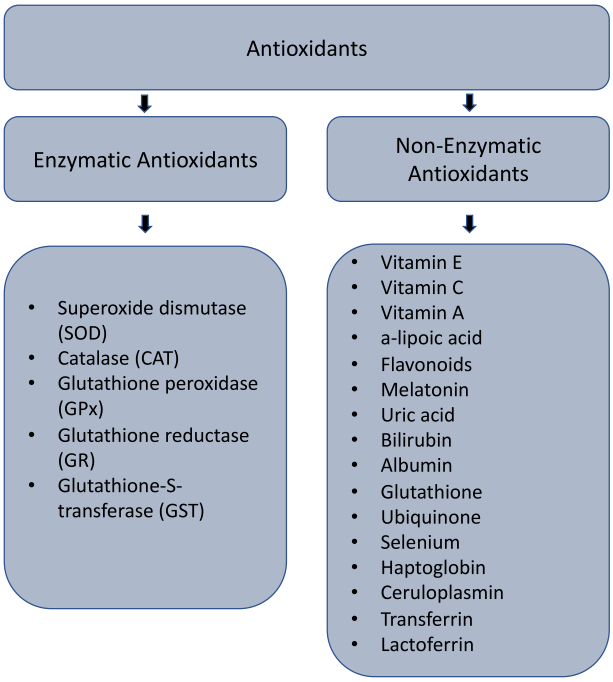

Fig. 2. Enzymatic and non-enzymatic antioxidants.

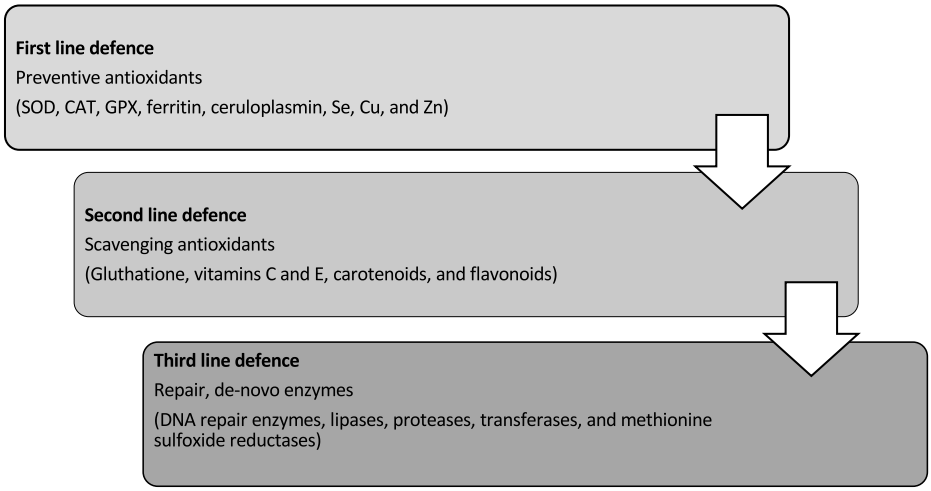

Fig. 1. The antioxidant defense system comprises different functional groups that can be grouped into three lines of defense.

or GSH/GSSG ratio is closely related to susceptibility to oxidative stress and carcinogenesis while high GSH levels elevate the antioxidant potential of various tumor cells, increasing their resistance to oxidative stress (Traverso et al., 2013; Marengo et al., 2016).

GSH and the GSH-related enzyme system can significantly affect the sensitivity to chemotherapeutic agents in patients with primary and recurrent glial tumors (Backos et al., 2012). Studies have shown that a change in the enzyme system related to GSH and an increased GSH level may lead to drug resistance in UWR-2 human malignant astrocytoma cells and different human medulloblastoma cell lines including Daoy, D283 Med, D341 Med, D384 Med, D425 Med, and D458 Med cells (Ali-Osman et al., 1989; Friedman et al., 2002). In addition, *in vitro* studies on UWR-2 cells revealed a relationship between chemotherapeutics and cellular GSH content (Ali-Osman et al., 1989, 1990). In fact, in an *in vitro* study, alantolactone, a sesquiterpene lactone, is considered a promising agent for glioblastoma therapy due to its ability to suppress proliferation of human glioblastoma cell lines such as U-87, U-373, and LN-229, induce cell death and decrease GSH levels (Khan et al., 2012).

Vitamin E, vitamin C and carotenoids are among the antioxidant foods consumed with the diet. They also have antioxidant properties as well as anti-inflammatory properties like other bioactive phytochemicals. Phytochemicals consist of various bioactive groups including phenolic acids and their derivatives, flavonoids and different types of coumarins and tannins (Liu, 2004). Phenolic antioxidants like curcumin, resveratrol and genistein have recently been attracting attention in promising trials for future cancer prevention purposes towards the colorectal adenomas and carcinomas, gastric and esophageal cancers (Gescher et al., 2001; Gullett et al., 2010). These phenolic chemicals have both antioxidant and anti-inflammatory activities (Djuric et al., 2001; Leu and Maa, 2002; Brisdelli et al., 2009).

The potential therapeutic effect of resveratrol has been studied in many types of cancer, including glioma-type brain tumors and many inhibitory properties have been demonstrated, such as blocking the activation of carcinogens and inducing their detoxification, thus preventing ROS damage and attenuating inflammatory responses (Aggarwal et al., 2004; Fulda and Debatin, 2006; Shankar et al., 2007; Gagliano et al., 2010). It has been shown to induce various responses to resveratrol in human U-251 glioma cells, depending on the sulfonation activity associated with the brain (Gagliano et al., 2010). It has also been shown that its combination with the alkylating agent temozolomide increases the efficacy of CT for glioblastoma-initiating cells from GBM patients (Herst et al., 2012; LI et al., 2016). Resveratrol has been shown to be valuable in personalized treatment of GBMs due to findings from *in vitro* studies using human LN-229 and U-251 GBM cell lines (Sun et al., 2012). Also, epigallocatechin-3-gallate (EGCG) in combination with temozolomide elevates the potency of therapies for brain tumors in orthotopic mouse glioblastoma (using U-87, U-251, and LN-229 cells) models (Chen et al., 2011). Curcumin exhibits antitumorigenic potential via suppressing the formation of B16F10 mouse melanoma cells generated brain tumors in mice and it may block proteins involved in the initiation of protective signals (Purkayastha et al., 2009).

In vivo anticarcinogenic properties of oleuropein and hydroxytyrosol were investigated on rat C6 astrocytoma spheroid implantation glioma model and their antioxidant and non-enzymatic effects were analyzed via the use of biochemical biomarkers. According to the results both molecules could inhibit lipid peroxidation and protein oxidation in cultured rat C6 glioma cells and C6 rat glioma model (Martínez-Martos et al., 2014). Cellular antioxidant and methylation metabolism is associated with the transsulfuration pathway that modify homocysteine, an intermediate of the methionine cycle, to cysteine, by inhibiting glutathione synthesis. For instance, N-acetylcysteine can neutralize mutagenic molecules and prevent cancer progression, lipoic acid can regulate glutathione biosynthesis and taurine can enhance regeneration in oxidant induced injuries by sequestering cytotoxic agents (Mates, 2012).

2.2. Enzymatic antioxidant defense systems

Endogenous defense mechanisms are formed by various enzyme systems that catalyze reactions that neutralize free radicals. In this way, they protect the cells from damage caused by free radicals. Three major classes of antioxidant enzymes, superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) are important detoxifying enzyme systems.

SOD functions by quenching superoxide radical (O_2^-). Superoxide is the cardinal ROS generated from different origins, so its degradation by SOD is of primary significance for every cell. SOD is found in three different forms: copper/zinc SOD or SOD1, manganese SOD or SOD2, and extracellular SOD or SOD3. The role of SOD in cancer has been discussed with different aspects with recent studies. Since SOD is localized in different cells, each SOD may be specialized for a different function. SOD1 is known to be closely related to cancer. The loss of SOD1 elevates the level of ROS, which causes DNA impairment and promotes tumorigenesis. In addition, antioxidants such as SOD1 are needed to prevent excessive cellular damage and apoptosis because cancer cells have higher ROS levels. In early studies, SOD2 expression was shown to be reduced in tumors, which led to SOD2 being considered a tumor suppressor (Oberley and Buettner, 1979). However, since the recent results show heterogeneity, it is thought that SOD2 activity may vary depending on the stage/tumor type (Hempel et al., 2011; Dhar and St Clair, 2012). Finally, the role of SOD3 in cancer is less understood. Since it is extracellular localized, its effect on pancreatic ductal adenocarcinoma occurs through the tumor microenvironment (Che et al., 2016).

Catalase is a peroxisomal enzyme that reduces hydrogen peroxide to water. Catalase failure may result in increased ROS levels and oxidative damage. Catalase has a protective and anti-apoptotic function by eliminating ROS (Jeong and Joo, 2016). Results from several studies investigating the relationship between catalase and cancer provided conflicting explanations. Catalase activity may provide resistance to oxidative stress induced by ascorbic acid in cultured U-251, U-87 and U-13898 human glioblastoma cells (Klingelhoeffer et al., 2012).

GPx is another group of enzymes that can convert hydroperoxides into water. The presence of an active GPx is a key factor determining susceptibility to oxidative stress. Despite the presence of catalase activity in cells, ROS can cause increased cell death. This is due to decreased or a lack of detectable GPx expression, indicating their dependency for GPx for detoxification of free radicals (Dokic et al., 2012a). In a study made on patients with GBM and transitional meningioma, it has been shown that levels of GPx and glutathione reductase (GRx) decreased significantly (Tanriverdi et al., 2007). In GBM cells, lack of GPx1 expression and activity was demonstrated and it has been highlighted that GPx1 is a critical antioxidant enzyme for modulation of oxidative damage in GBM cells (Dokic et al., 2012b).

3. The advantages and limitations of antioxidant use against GBM: from preclinical perspectives

There is a constant demand for new treatments to prevent cancer, a disease that seriously affects human life globally. The interest of research on cancer treatment is beginning to tend with naturally derived antioxidant compounds as they are thought to have less toxic side effects comparing to existing treatments, such as the use of chemotherapeutic agents (Greenwell and Rahman, 2015). Plant metabolites with antioxidant properties can be shown as naturally occurring sources that are researched for their anticancer activities. With the success of these metabolites converted into essential drugs for cancer treatment, they stand out as new technologies to further develop the antioxidant drug industry (Wall-Medrano and Olivas-Aguirre, 2020). With the development of pharmaceutical technologies, nanotechnological drug systems that control the release of plant-based antioxidant drugs, research application methods and the aim to increase anticancer activities have

been established (Sivaraj et al., 2014). According to the current knowledge, oxidative DNA damage is the origin of the first stage of carcinogenesis. For instance, reactive oxygen species (ROS) can create changes in pyrimidine and purine structures and cause breaks in DNA what is called mutagenicity. However, dietary antioxidants like carotenoids, vitamin E or flavonoids can prevent these mutagens that stimulate carcinogenicity by enhancing gap-junctional communication, inhibiting protein kinase C activity and modulating phase I and II xenobiotic detoxification, respectively (Elliott, 2005; Moon et al., 2006; Aggarwal et al., 2010). Also, other studies showed that different antioxidant applications like curcumin, resveratrol, fish oil and selenium yeast restored tumor inhibited CD4+/CD8+ T cell proliferation, increased apoptosis, memory T cells and Treg cell expansions (Yang et al., 2008; Bhattacharyya et al., 2010; Wang et al., 2013; Sahu et al., 2016). Moreover, it is important to maintain oxidation and antioxidation homeostasis to keep healthy biological systems. There is also a reality for the double-edged effect of antioxidants besides oxidant molecules. Physiologic concentrations of external antioxidants are necessary to keep redox balance for healthy cells. On the other hand, excessive doses of antioxidants can obstruct and distort redox balance which gives rise to cytotoxic or genotoxic either (Bouayed and Bohn, 2010; Olivier et al., 2021).

Although there have been many literature data about anticancer properties of several natural or synthetic antioxidant sources in cell culture and animal studies (Togar et al., 2015; Cacciatore et al., 2017; Özgeriş et al., 2017; da Nóbrega et al., 2018; Emsen et al., 2016; 2018; 2019; Koc et al., 2018; Turkez et al., 2018; 2019; Yazici et al., 2020; Özdemir et al., 2020; Colapietro et al., 2020; Pathak et al., 2020), there has not been a single natural polyphenol with antioxidant properties that was registered or approved for clinical use as an anti-GBM drug (Greenwell and Rahman, 2015; Paller et al., 2016). It was also reported that dietary antioxidant use didn't show a consistent result in clinical trials and needed to be investigated in a wider spectrum of GBM patients (DeLorenze et al., 2010). There are several reasons for the difficulties in using natural antioxidants in the pharmaceutical industry. If plant species are used as an anticancer source, it would be difficult to extract and used as an anticancer drug candidate for companies. There are several complexities for this case that one of the most important difficulties is the lack of patentability of plant extracts. Also, production periods, batch consistency and variation in compositions make the natural antioxidant industry challenging. Moreover, standardization in active ingredients for naturally obtained antioxidants makes it difficult to produce on large scales. Another obstacle for the natural antioxidant industry is the lack of information about the exact constituent and composition of plant sources resulted from variation in climate change, soil quality and cultivation techniques (Mustapa et al., 2015; Tungmunnithum et al., 2018; Oyenihi and Smith, 2019). Furthermore, different *in vitro* cell line models are used to stimulate the GBM disease environment and physiology. One of the most common cell line models is a rat glioma cell line (C6) which has been called the gold standard for GBM studies (Giakoumettis et al., 2018). C6 cell line models for GBM studies are generally used to investigate various biological properties of brain tumors, such as tumor invasion and migration, growth factor regulation and production tumor growth, angiogenesis, and blood-brain barrier deterioration (Hacioglu et al., 2021; Kacar et al., 2021; Kar et al., 2021). In this regard, the variability of medium and/or serum components due to batch may give rise to low reproducibility of generated *in vitro* data. Moreover, the several growth factors like glial growth factor and transforming growth factor β1 in the content of serum may incline unwanted binding features and ostensible activation or inactivation properties by the antioxidant molecules (Ledur et al., 2017).

4. The efficacy of concomitant application of certain antioxidants in patients with GBM in clinical trials

There are a limited number of studies for assessing the efficacies of a concomitant administration of antioxidants in patients with glioblastoma treated with several RT and CT strategies. These previous studies were summarized in Table 1. Melatonin, a natural chrono-biotic compound, is known for its strong immune-boosting, anti-inflammatory and antioxidant properties. The co-administration of melatonin was suggested to reduce side effects by chemotherapeutics, enhanced the cytotoxic action by chemotherapeutic agents and decreased drug dosages in GBM cases. Indeed the patients with GBM who received RT (60 Gy) plus melatonin (as 20 mg/daily orally) led to higher survival as compared to patients treated with RT alone (Lissoni et al., 1996). Moreover, the combined use of melatonin and *Aloe vera* (1 ml twice/-day) enhanced the percent 1-year survival in GBM patients with advanced solid tumors in comparison to patients treated with only melatonin (Lissoni et al., 1998). Similarly to melatonin and *A. vera*, oral lycopene (8 mg/daily) supplementation with RT provided significant potential therapeutic benefit in the clinical trial (Puri et al., 2010). Again, the clinical use of trans sodium crocetinate (0.25 mg/kg), a synthetic small-molecule exhibiting antioxidant feature, along with the temozolomide (TMZ, 75 mg/m^2) and RT (2 Gy) (Gainer et al., 2017). On the contrary, the co-application of beta carotene, a natural retinol (vitamin A) precursor, with mitomycin-C and RT (60 Gy) was found to be unprofitable in GBM cases (Stewart et al., 1997). Clinical trials revealed that antioxidants did not produce additional side effects along with the undesirable effects of RT or CT. In addition, a study was conducted to investigate the survival effects of dietary intake of antioxidant vitamins and nutrients in 814 glioblastoma multiforme patients. The

Table 1
Gene pathways that related to the GBM formation and possible oxidant or antioxidant molecules that could ameliorate effects of the gene cascade on the disease pathology.

Gene pathways	Mechanism	Mode of Action	Compound
Isocitrate dehydrogenase (IDH)	Oxidative stress	Inactivation	diethylamine NONOate, S-nitrosothiols, 3-morpholinosydnomine N-ethylcarbamide superoxide dismutase, spermine NONOate, oxalomalate, peroxynitrite, hydrogen peroxide, potassium superoxide
Acid ceramidase (ASAH1)	Antioxidant	Inhibition	desipramine, benzoxazolone carboxamide
Notch pathway	Antioxidant	Inhibition	quercetin, epigallocatechin-3-gallate (EGCG), crocin
Platelet-derived growth factor (PDGF)	Antioxidant	Inactivation	Delphinidin, (−)-epigallocatechin-3-gallate, Lutein, caffeoyl-prolyl-histidine amide
Vascular endothelial growth factor (VEGF)	Antioxidant	Inhibition	ellagic acid, gallic acid, tangeretin, baicalein, nobiletin, baicalin
PI3K/AKT/mTOR pathway	Antioxidant	Inhibition	delphinidin, resveratrol, apigenin, neferine, plumbagin
Epidermal growth factor receptor (EGFR)	Antioxidant	Inhibition	benzimidazole, quinoxaline derivatives, silibinin
Sonic hedgehog (SHH) signaling pathway	Antioxidant	Inhibition	cyclopamine, sulforaphane, quercetin

results of this study did not show a consistent relationship between dietary antioxidant/vitamin supplements and survival (Il'yasova et al., 2009). The application of antioxidants for elevating the efficacy of anti-GBM treatment can be considered safe. But their therapeutic potencies or contributions could be different due to different causal factors involving bioavailability, BBB permeability, mode of action, interaction with drugs as well as preferred application dosages.

5. Potential signaling pathways associated with pathogenesis of GBM: focusing on antioxidant mechanisms

It is already known that the pathogenesis of GBM is closely related to genetic background and gene expression alterations. Different factors like cellular and environmental can differentiate gene expression patterns and disease-related pathways greatly (Montemurro, 2020; Su et al., 2018). Thus, it has great importance to investigate and discuss various pathways and gene families that can result in cellular transformation and GBM formation. In this section, potential genes that are related to GBM occurrence and treatment for the disease through these genes were discussed.

One of the potential genes that can cause GBM formation is the isocitrate dehydrogenase (IDH) gene which plays an important role in the citric acid cycle enzymatic reactions. There are three different isoforms of the IDH enzyme (IDH1, IDH2, and IDH3). Two of these enzymes (IDH2 and IDH3) are located in the matrix of mitochondria and one of them (IDH1) is positioned in the cytoplasm and peroxisome. IDH1 and IDH2 enzymes convert $NADP^+$ and isocitrate into carbon dioxide, NADPH and α -ketoglutarate (α-KG) via the oxidative decarboxylation reaction (Fedøy et al., 2007). This multistep process is reversible and begins with isocitrate oxidation from oxalosuccinate and decarboxylated oxalosuccinate finalized to α-KG which is used for enzyme cofactors (Kaminska et al., 2019). Secondary glioblastoma analyses have been shown that IDH mutations exist in all of the cancer cases but, rarely found in 22 human GBM samples (Parsons et al., 2008). These mutations can include a gain or loss of function of enzymatic activity of IDH which may result in the accumulation of isocitrate (loss of function) or 2-hydroxyglutarate (2-HG) (gain of function) that lead to carcinogenesis (Cohen et al., 2013; Turkalp et al., 2014). Treatment of GBMs through IDH genes is generally focused on inhibition of the gene to prevent over-accumulation of 2-HG molecules that prevent the growth of the U-87 glioma cells (Popovici-Muller et al., 2018). Thus, there have been extensive studies to discover IDH gene inhibitors to prevent tumorigenesis (Rohle et al., 2013; Di Stefano et al., 2015; Dang and Su, 2017; Huang et al., 2019). The previous study has claimed that nitric oxide (NO) donors like diethylamine NONOate, S-nitrosothiols, 3-morpholinosydnomine N-ethylcarbamide (SIN-1)/superoxide dismutase and spermine NONOate have been shown to inactivate IDH activity through oxidative stress in a time and dose-dependent manner (Yang et al., 2002). Another oxidative molecule, oxalomalate, has been shown to inhibit cytosolic IDH activity and it has been called a competitive inhibitor of the IDH enzyme (Yang and Park, 2003). Also, various oxidative agents such as peroxynitrite, hydrogen peroxide and potassium superoxide have been shown in several studies to block the activity of IDH enzyme through oxidative mechanisms (Lee et al., 2001, 2003).

Furthermore, ceramide signaling has been shown to be an important player in tumorigenesis formation in GBM. In the pathway, acid ceramidase (ASAH1) metabolizes ceramides and produces free fatty acids and sphingosine. It is known that sphingosine-1-phosphate (S1P) enhances proliferation and cell survival of U-87 and pediatric glioblastoma (SJGBM2) cells which can increase cancer risk (Doan et al., 2017). On the other hand, ceramides have been shown to activate cell death and senescence mechanisms in pancreatic and breast cancers and leukaemias (Morad and Cabot, 2013). GBM analyses have shown that glioma cells have more concentration of S1P than ceramide which lowers the apoptotic cell death ratios and increases cell proliferation to enable glioma cells for spreading freely. Also, ASAH1 gene differentiation has been analyzed to increase glioblastoma malignancy status of U-87 cells and allow them to have higher concentration; spread in the nearby tissue (Nguyen et al., 2018). Desipramine, an antidepressant drug with antioxidant properties, was shown to have an inhibitory effect on ASAH1 enzyme inhibition (Elojeimy et al., 2006; Vircheva et al., 2012). Another ASAH1 inhibitor, benzoxazolone carboxamide, was also claimed to have antioxidant properties because of benzoxazolone ring structure (Bach et al., 2015; Verma and Silakari, 2018).

The other candidate gene family that can be used for gene-based GBM therapy is the Notch signaling component. Notch signaling is of crucial importance in cell proliferation, differentiation and apoptosis in the central nervous system (CNS), and any abnormality in the pathway mechanism can lead to carcinogenesis and GBM formation (Miele et al., 2006). In the Notch pathway, four main receptor plays important role in tumorigenesis. Notch-1 can show oncogenic or tumor suppressor properties with respect to tissue type and it has been shown to be closely related to glioma progression and malignant phenotype (Yan et al., 2019). Previous studies have shown that targeting the Notch pathway for GBM treatment can prevent *in vitro* and *in vivo* tumor growth and progression because stem-like glioma cells have been investigated to express notch signaling genes extensively (Fan et al., 2009). Also, targeting Notch pathway players like Hes1, Hey 2 and Hey 3 inhibitors have been shown to be effective for stem cell pool loss, differentiation and cell growth arrest in human glioblastoma neurosphere lines including HSR-GBM1A, HSR-GBM1B, GBM-DM140207, GBM-KK190156 and JHH551(Ying et al., 2011). Different antioxidant molecules such as quercetin, epigallocatechin-3-gallate (EGCG) and crocin have been proved to inhibit Notch signaling cascade in animal model of diabetic nephropathy and hepatocellular carcinoma (HCC) as well as Atoh1/GFP transgenic mice via affecting various elements in the pathway (Gu et al., 2015; Salama et al., 2019; Amin et al., 2020).

Platelet-derived growth factor (PDGF) has turned out to be an important target for GBM treatment because the PDGF pathway can enhance survival and proliferation in all grades of human gliomas (Pearson and Regad, 2017). In healthy glial cells, PDGF ligands bind to its receptor (PDGFRα and PDGFRβ) which is a receptor tyrosine kinase (RTK) placed on the cell surface and start the transduction cascade. After interacting with a ligand, the receptor is dimerized and phosphorylates tyrosine residues on several subunits. This phosphorylation leads the downstream cascade elements that finally reach the genome and activates DNA synthesis and cellular proliferation (Nazarenko et al., 2012; Heldin, 2013). Besides, an autocrine PDGF loop is enhanced in GBM that must be inactive in healthy brain cells. Also, several *in vitro* and *in vivo* studies have shown overexpression of PDGF ligands in GBM and mutated, amplified and modified PDGF receptors have been investigated in GBM tumors that the receptor plays a crucial role in tumorigenesis (Popescu et al., 2015; Westermark, 2014; Cantanhede and de Oliveira, 2017). Inhibition of PDGF signaling cascade was shown to be an important target for the anticarcinogenic property. Delphinidin, a dietary anthocyanidin and an antioxidant were shown to have an *in vitro* inhibitory effect on the PDGF pathway through PDGFR blockade (Lamy et al., 2008; Chen et al., 2019). Various antioxidant molecules like (−)-epigallocatechin-3-gallate, lutein and caffeoyl-prolyl-histidine amide were shown to inhibit PDGF signaling cascade (Chen and Zhang, 2003; Kwak et al., 2014; Lo et al., 2012).

Studies have shown that another important candidate target for GBM treatment is vascular endothelial growth factor (VEGF) which is a cytokine used for activating angiogenesis and restoring oxygen supply through new blood vessels growth. In the case of hypoxia, the VEGF signaling pathway is activated so that the pathway is called hypoxia-inducible signaling. Activation of VEGF signaling stimulates the tyrosine kinase pathway and finally enhances the angiogenesis process (Apte et al., 2019). VEGF pathway also has an important role in enhancing angiogenesis in GBM to promote survival from external stress and functional optimization for the environment. The vascular sources are crucial for maintaining the glioblastoma tumor growth and receive

supplements from the bloodstream (Jhanwar-Uniyal et al., 2015). Thus, it can be an effective strategy that preventing angiogenesis via the inhibition of the VEGF pathway for anticancer treatment. Several VEGF pathway inhibitors have been shown to be effective for treatments of various cancer types including metastatic colorectal and medullary thyroid cancers, neuroendocrine tumors, and GBM (McIntyre and Harris, 2015; Zirlik and Duyster, 2018). Although VEGF inhibitor therapies have been shown beneficial and widely used for cancer treatments, drug resistance mechanisms and overall survival advantages haven't been comprehensively studied yet. Moreover, anti-VEGF treatment combination with immunotherapy, receptor tyrosine kinase inhibitors (TKIs), cytotoxic drugs and RT approaches have been shown promising results against GBM using *in vitro* (GL-261 mouse glioma cells) and *in vivo* (intracerebral GBM mouse models) approaches and surgical tissue samples from patients with recurrent glioblastoma (Lu et al., 2012; Okuda et al., 2017; T. T. Liu et al., 2018). Several antioxidant molecules were shown to have an inhibitory effect on the VEGF signaling. For instance, ellagic acid, a natural phenolic antioxidant, was shown to have inhibitory function against PDGF-induced phosphorylation and migration in U-87 cell cultures (Priyadarsini et al., 2002; Labrecque, 2005). Also, several other antioxidant plant phenolics as gallic acid, tangeretin, baicalein, nobiletin, and baicalin were investigated to exert an inhibitory effect against VEGF signaling (HE et al., 2015; 2016).

One of the most important intracellular pathways that have a vital role in cell cycle regulation is the PI3K/AKT/mTOR pathway. Phosphatidylinositol 3-kinases (PI3Ks), key elements of the pathway have been shown to phosphorylate serine/threonine-specific protein kinase (AKT) and active its function. Activated AKT stimulates the mammalian target of rapamycin (mTOR) which has been found to elevate glial cell proliferation through activation of ribosomal protein S6 kinase (S6K) and eukaryotic translation initiation factor 4 E binding protein 1 (E4BP1) (Conciatori et al., 2018; Mecca et al., 2018). In addition, overstimulated the PI3K/AKT/mTOR pathway has been analyzed to be responsible for GBM aggressiveness and reduction of cancer patient's survival rate (Lino and Merlo, 2011; Mantamadiotis, 2017). The phosphate and tensin homolog (PTEN) is an effective candidate that can be used against GBM disease by inhibiting the PI3K pathway. Also, PTEN blocks AKT activity through its lipid phosphatase property (Janbazian et al., 2014). For GBM cases, the PTEN gene has been shown to be inactivated because of the mutations. Double mutations in the PTEN alleles are sufficient to enhance uncontrolled cell proliferation and tumorigenesis. Also, reports have been investigated that PTEN activity makes U-87 and U-251 glioma cells sensitive against RT and CT (Lester et al., 2017; Romano and Schepis, 2012). Thus, the PTEN gene cascade is thought to be a good candidate for GBM treatment and therapy. According to the literature data, antioxidants like delphinidin, resveratrol, apigenin, neferine and plumbagin showed excellent inhibitory effect on the PI3K/AKT/mTOR pathway in the aspect of different mechanisms (Jiang et al., 2009; Poornima et al., 2013; Li et al., 2014; Chamcheu et al., 2017; Yang et al., 2018; Turkez et al., 2021).

Moreover, the epidermal growth factor receptor (EGFR) is also a transmembrane RTK which is activated via the binding extracellular signals like transforming growth factor-α or epidermal growth factors. In health glial cells, the inactive monomer form of receptor turns into a homodimer active form and induces the tyrosine kinase activity of the intracellular domains. This activation starts a series of transduction cascades that ultimately result in cell proliferation, DNA synthesis, adhesion and migration (Ohgaki and Kleihues, 2007; Wee and Wang, 2017). EGFR mutations have been found to be an important factor for GBM pathogenesis and EGFR amplification has been shown to be the main player for primary GBMs. Generally, tyrosine kinase inhibitors (TKIs) have been utilized for the EGFR targeting against GBMs because of the challenging complexity of the signaling pathway (Kraus et al., 2002; Halatsch et al., 2004; Padfield et al., 2015). On the other hand, several antioxidant molecules were investigated to have an inhibitory effect on the EGFR signaling such as benzimidazole, quinoxaline derivatives and silibinin in *in vitro* experimental HCC, breast and colon cancer models (Kim et al., 2011; Li et al., 2011; Ahmed et al., 2020).

The last but not the least important candidate pathway for GBM therapy is the sonic hedgehog (SHH) signaling pathway. In healthy glial cells, signaling cascade start with binding and inhibiting of SHH glycoprotein to patched 1 protein and co-receptors for activation of Smoothened (SMO) protein. After the activation of SMO, it leads to targeting of glioma-associated transcription factors (GLIs) to the nucleus and enhancing angiogenesis, proliferation, stem cell self-renewal and epithelial-to-mesenchymal transition. Overactivity of SHH cascade leads to stem cell transformation into glioblastoma stem cells through Patched1 or SMO mutation (Gupta et al., 2010; Takezaki et al., 2011). Various studies showed that different antioxidant molecules like cyclopamine, sulforaphane and quercetin have inhibitory properties against SHH signaling cascade (Rodova et al., 2012; Zhao et al., 2014; Guo et al., 2020). Gene pathways associated with the formation of GBM and oxidative mechanisms were summarized in Table 2 and natural antioxidants that were investigated against GBM in non-clinical studies were shown in Table 3.

6. Challenges for GBM therapies with antioxidants

Oxidative stress could take two opposite roles in cancer-targeted therapies. First, high ROS levels can induce apoptosis or apoptotic-related mediators for antitumor therapy. Second, reduction in ROS concentration by anti-oxidative factors could lead to the promotion of tumorigenesis. Therefore, oxidative stress and related signaling pose a great challenge for anticancer therapies (Sosa et al., 2013; Mortezaee, 2018). Indeed, tumor cells are susceptible to any changes in intracellular redox states, particularly to the concentration of ROS (Lu et al., 2017). ROS can have both pro-tumoral and anti-tumoral effects via inhibiting or activating tumor-promoting mediators (Kim et al., 2008; Liu et al., 2008). The moderate ROS level produced by cancer cells induces hypoxia, and numerous studies have demonstrated that this process plays a key role in the progression of cancer (Albini et al., 2018; Biancur and Kimmelman, 2018; Fels et al., 2018; Joseph et al., 2018; Tan et al., 2018; Tzeng et al., 2018). By contrast, high ROS concentration could suppress the release of hypoxic mediators from tumor cells (Biancur and Kimmelman, 2018; Y. Y. Liu et al., 2018). Interestingly, hypoxia could act as an inhibitor of ROS production via modulating the immune system for regression of tumor (Fig. 3) (Biancur and Kimmelman, 2018).

Most studies have suggested that disruption of the redox balance in cancer is a promising therapeutic strategy via using either oxidative or

Table 2
The summary of outcomes from clinical trials of GBM cases using antioxidant supplementation.

Antioxidant	Treatment type	Patient number in clinical trial	Outcome	Reference
Melatonin	RT plus melatonin	30	Prolonged survival time, improved the life quality	Lissoni et al. (1996)
Beta carotene	CT plus RT plus beta carotene	11	No benefit	Stewart et al. (1997)
Melatonin and *Aloe vera*	Melatonine plus *A.vera* plus RT	50	Stabilization of disease, increased survival percent	Lissoni et al. (1998)
Lycopene	Lycopene plus RT plus PT	50	Elevated survival percent	Puri et al. (2010)
Trans sodium crocetinate (TSC)	TSC plus RT plus TMZ	50	Combatted hypoxia in tumor tissue, increased survival percent, improved the life quality	Gainer et al. (2017)

Table 3
Natural antioxidant that have anticarcinogenic effects against glioblastoma investigated in non-clinical studies.

Antioxidants	Anticarcinogenic properties	Reference
Andrographolide	Blocks cell cycle	Lo et al. (2012)
Berberine	Enhances apoptosis	Liu et al. (2015)
Betulinic acid	Enhances apoptosis	Schmidt et al (1997)
Deoxypodophyllotoxin	Blocks cell cycle and enhance apoptosis	Guerram et al. (2015)
Ginsenoside	Inhibits cell cycle and angiogenesis	Wu et al. (2011)
Icariin	Enhances apoptosis and inhibits cell proliferation	Yang et al. (2016)
Jaceosidin	Blocks cell cycle and enhance apoptosis	Khan et al. (2012)
Mistletoe lectins	Gene expression regulation	Schötterl et al (2017)
Oridonin	Enhances apoptosis	Lin et al. (2015)
Plumbagin	Blocks cell cycle and enhance apoptosis	Khaw et al. (2015)
Procyanidins	Prevents invasion	HE et al. (2015)
Quercetin	Inhibits cell proliferation	Michaud-Levesque et al. (2012)
Resveratrol	Blocks cell cycle	Yuan et al. (2012)
Rutin	Inhibits angiogenesis and cell migration	Freitas et al. (2011)
Saponin-1	Blocks cell cycle and enhance apoptosis	Li et al. (2013)
Saponin-6	Blocks cell cycle and enhance apoptosis	JI et al. (2016)
Saponin-B	Blocks cell cycle and enhance apoptosis	(Wang et al., 2013)
Shikonin	Inhibits invasion and migration and	(Li et al., 2014)
Silibinin	Enhances apoptosis	Chakrabarti and Ray, (2015)
Thymoquinone	Inhibits autophagy	Racoma et al. (2013)
Trichosanthin	Inhibits cell proliferation	(J et al., 2015)
γ-Mangostin	Enhances Apoptosis	HF et al. (2010)

anti-oxidative therapies. These therapies should be able to specifically target cancer cells without affecting non-cancer cells or tissues around the tumor. Also, the activity of tumor suppressor cells within the tumor microenvironment is needed to be maintained in patients receiving such approaches (Farhood et al., 2019).

For a long time, antioxidants are known as free radical destroyers and beneficial dietary nutrition. But in last years, it has been begun to be believed that antioxidants could raise carcinogenesis in various situations (Watson, 2013). Detailed studies are required on their ability to threaten the human intestinal microbiota at the colon level, their bio-transformation, the extremely low bioavailability of natural antioxidants, their ability to cause problems with their adsorption and application capacity in circulating metabolites by certain tissues (Russo et al., 2017). Moreover, there should be a clear line between cancer prevention and treatment to understand the best-suited use of antioxidants for carcinogenesis. Thus, it is important to understand possible mechanisms for the specific antioxidants in cancer treatment and their anticarcinogenic properties for cancer prevention to make it possible for constituting a comprehensive description of the use (Seifried et al., 2003). Also, another concern about antioxidants is raised because of their bioactivity levels. Their natural structures make them difficult to modify chemically and increase their anticancer activity in lower concentrations. Because of this situation, the application of antioxidants in higher concentrations could lead to toxicological features against low anticarcinogenic effects (Forman et al., 2014).

7. Future directions for Anti-GBM therapy with antioxidants

Although therapeutic approaches for the GBM treatment have been advancing increasingly, survival rates have not been expanded sufficiently. It has become clearer than ever that improved therapeutic approaches and novel strategies should be integrated into the GBM treatment. Recent advancements explored novel approaches in various areas like precision oncology, immunotherapy and single-cell approaches. Besides, the accumulation of information about the GBM mechanism and the relationship between disease formation and genetic background made it possible to understand the true nature of the disease comprehensively. Thus, it would be possible to increase survival rates for patients with fewer side effects by using this information. Also, integrating other factors like the immune system, blood-brain barrier and solid tumor structures into therapy could solve the most important problems for the disease. Multiple-sided therapies for GBM treatment could be more efficient than traditional anticancer treatments like immune therapy and antioxidant integration or pathway targeted oxidant application and RT. Also, it is known that the positive impact of different antioxidants on immunological response in various carcinomas. Immunotherapy and antioxidant combined treatments have been a promising application for GBM tumorigenesis. Not only life expansion is one of the

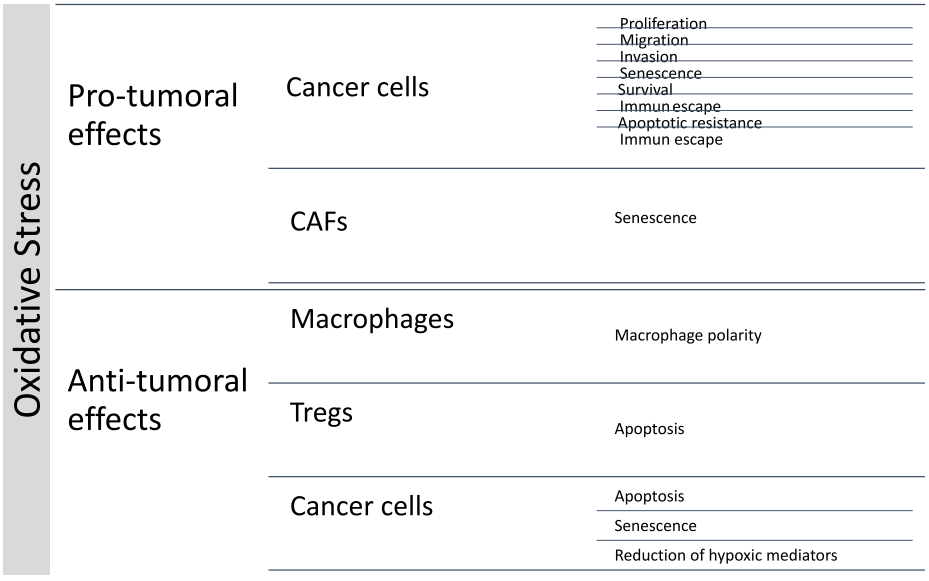

Fig. 3. Pro- and anti-tumoral effects of oxidative stress. Cancer cells and cancer associated fibroblasts (CAFs) are directed to tumorigenesis by oxidative stress. On the contrary, oxidative stress could target macrophages, regulatory T cells (Tregs) and cancer cells for inhibition of cancer (Gagliano et al., 2010).

most important factors to choose a treatment option, but also elevating the quality of life for the patients remains another crucial component that needs to be considered intensively. Integrating antioxidants into GBM therapies probably would decrease anticancer agent dose and treatment intervals so that the patient life standard would be expanded in parallel with survival rates.

Author contributions

Conceptualization, H.T. and A.M.; writing-original draft preparation, O.O.T. and M.E.A.; writing-review and editing, H.T., O.O.T. and M.E.A.; supervision, H.T. and A.M. All authors have read and agreed to the published version of the manuscript.

Declaration of interestsDOCI

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper entitled "**Safety and Efficacy Assessments to Take Antioxidants in Glioblastoma Therapy: From In Vitro Experiences to Animal and Clinical Studies**".

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