Chapter 11

Antioxidant Supplementation during Glioma Therapy: Friend or Foe?

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Additional information is available at the end of the chapter

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Abstract

Gliomas which are one of the most common types of primary brain tumors are originated from glial cells. Type of tumor and tumor location are the most important factors to determine the treatment options. The treatment options might be surgery, radiation therapy, chemotherapy, targeted therapies, and experimental clinical studies. Especially, in course of chemotherapy and radiotherapy, antioxidant levels decrease. Antioxidants fight against the oxidants' negative effects, which include cell damage, oxidative stress, and so on. Recent years, some researchers present that the antioxidant using could be harmful in some cases. A growing body of evidence suggests that antioxidant supplementation might increase the mortality. In this chapter, an overview of antioxidants and their functions has been presented to introduce researchers to the changes and effects of the antioxidants in glioma treatment. The evidence-based studies have been summarized. These experimental studies are important to understand the right option for the patient and transfer the solution from bench to bed.

Keywords: glioma, treatment, antioxidant, oxidative stress, experimental studies

1. Introduction

Central nervous system tumors start in the brain or spinal cord [1]. The common symptoms of these tumors are headache, seizures, weakness, nausea, vomiting, and altered mental status [1, 2]. Gliomas are one of the most common primary brain tumors, which are originated from glial cells. In general, gliomas are classified astrocytoma, oligodendrogliomas, and ependymomas. According to World Health Organization (WHO), the histological classification of gliomas consists of astrocytoma, oligodendroglioma, oligoastrocytoma (low-grade gliomas)

and anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ependymoma, and glioblastoma (high-grade gliomas) [1–4]. The histological type of the tumor is the most significant thing to determine the treatment option [2].

Antioxidants are present in plant-based foods, for instance, some types of vegetables and fruits: wine, blueberry, different types of tea, grape, and so on [5, 6]. The main role of antioxidants is prevention of oxidants' harmful effects to human body. Principle regarding oxidant-antioxidant is related to a balance [7]. This balance's side determines the human body reaction. In case of elevated oxidant levels in organism body homeostasis is lost and oxidative stress occurs. Loss of this balance and oxidative stress lead some pathological situations: cancer, neurodegenerative diseases, cardiovascular diseases, immunological diseases, and so on [8–10]. In terms of these diseases with the antioxidant supplementation, cell damage can be fixed.

In this chapter, two different stories will be told and these stories will be turned one story. We will discuss some of the basic concepts of antioxidants, antioxidant systems and antioxidants supplementation and explain how antioxidant supplementation can help with the cancer therapy, especially glioma therapy. Experimental studies are summarized and present evidences are collected under three headings: in vitro studies, animal studies, and clinical trials.

2. What is antioxidant?

To understand the term antioxidant, we have to tell the story from the beginning. The story begins with oxygen. Oxygen is the main source of the life, but in the body oxygen sometimes acts like a foe. Oxygen has two unpaired electrons, which spin in the same direction [9]. For this reason, oxygen is a biradical, so it is a free radical. In general, free radicals are highly reactive compounds, which are called as "reactive oxygen species" (ROS). ROS are intracellular compounds, which consist of oxygen [7, 11]. The most known ROS are listed in **Table 1**.

Oxygen is less dangerous than oxygen-derived free radical species (superoxide, hydroxyl radicals, hydrogen peroxide, etc.), and they react with lipids, proteins, and nucleic acids [12, 13]. Besides ROS, nitrogen-derived molecules are present in human body. These are known as

Name	Molecule formula
Superoxide	O_2^-
Hydroxyl	$OH^\bullet$
Peroxyl	$ROO^\bullet$
Alcoxyl	$RO^\bullet$
Hydroperoxyl	$HO_2^\bullet$
Lipid peroxyl	$LOO^\bullet$
Hydrogen peroxide	H_2O_2

Table 1. Reactive oxygen species (ROS).

Endogenous sources	Exogenous sources
Normal cellular metabolism	UV
• Electron transport chain	Ozone exposure
• Neutrophils, macrophages	Hyperoxia
• Mitochondrial cytochrome oxidase	Burning organic foods
• Smooth muscle cells	Smoking
• Cortisol, catecholamine	Ionizing radiation
• Immune system cells	Air pollutants
	Heavy metal ions

Table 2. Endogenous and exogenous sources of ROS.

reactive-nitrogen species [6, 14]. These molecules can get involved with oxidant molecules, but all oxidants are not free radicals. They produce endogenously or with some exogenous sources' effects [9, 10]. Some endogenous and exogenous sources are shown in **Table 2**.

In human body, antioxidant systems are present to avoid cell damage due to free radicals. These antioxidant systems include a few enzymes for this reason they are called enzymatic antioxidants [9–11, 14]. The definition of antioxidant that it is a molecule reacts with free radicals and neutralizes them [6]. Except enzymatic antioxidants, generally, they occur naturally in foods, especially plant-based foods [15]. For instance, resveratrol is a very popular antioxidant in recent years, and it is found in grape, raspberry, blueberry, wine, and so on [16]. The most known non-enzymatic antioxidants are low-molecular-weight compounds such as vitamin C, vitamin E, beta-carotene, catechins, lycopene, glutathione, and coenzyme Q [5, 12, 17].

In summary, the story starts with oxygen and develops free radicals and stable molecules (DNA, protein, lipids, carbohydrates, etc.). Antioxidants are the good cops and they get involved the free radicals. In normal conditions, this is acceptable as happy ending. In terms of biological perspective, in course of normal metabolism energy production starts with consumption of oxygen and food nutrients. Oxygen and food enter the cell and mitochondria start to produce adenosine triphosphate (ATP). Free radicals form during cell's energy production. These free radicals are neutralized by antioxidant enzyme systems (superoxide dismutase, catalase, glutathione peroxidase, etc.) and non-enzymatic antioxidants [6]. In the presence of any pathological conditions, ROS are highly produced and although antioxidant enzyme systems and antioxidants try to eliminate them to protect the cell, they remain incapable. Redox balance breaks down, oxidative stress increases, and antioxidant levels decrease [14]. In terms of cancer, ROS imbalance is one of the hallmarks of cancer [18].

3. Antioxidants and cancer

Cancer is a malign disease, which is characterized by abnormal cell proliferation [19, 20]. The uncontrolled situation in the cell is a result of endogenous or exogenous effects. According to multistep carcinogenesis theory, cancer originated from one cell, so cancer is a monoclonal

disease and it develops in three stages. These stages are initiation, promotion, and progression [21]. Cells suffer damage with any endogenous or exogenous effects. Defects or mutations accumulate in the cell with these effects. The main effects are listed below [22]:

- Environmental factors,
- Lifestyle,
- Infections,
- Mutations,
- Inherited genetic diseases,
- Viruses
- Reactive oxygen species (ROS).

Aforementioned before ROS cause some pathological situations due to their reactive features [10]. They react with nucleic acids, proteins, lipids, and carbohydrates. As a result of this interaction, it is possible that cancer development may be from one cell. ROS may take a role any stages of carcinogenesis [7]. Proven roles of ROS on cancer progression [23]:

- Some genetic alterations are generated by ROS.
- ROS promote cell migration via invadopodia formation in vitro.
- ROS activate the PI3K/AKT/mTOR and MAPK/ERK mitogenic signaling pathways.

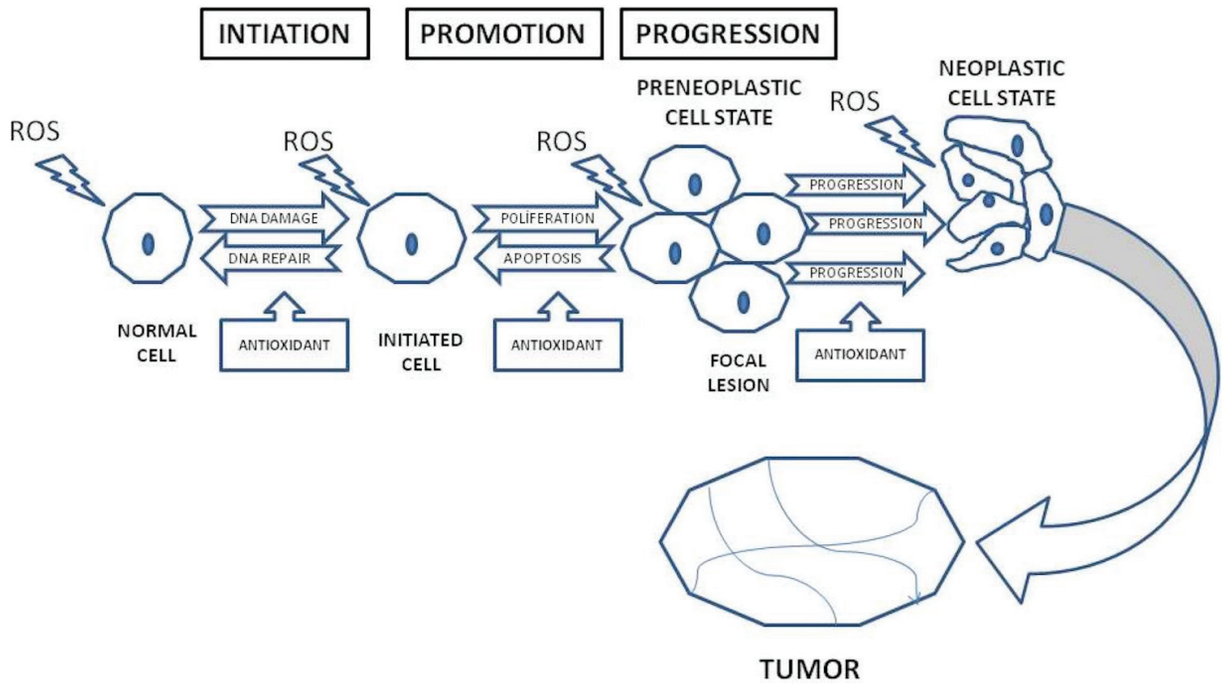

Figure 1. ROS-cancer relationship and antioxidant junction points.

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The main objectives of oncological treatment are increasing life-quality and extending survival time. When these objectives are considered, antioxidant supplementation brings to mind some questions. If clinicians add antioxidants to therapy:

- Does the success of therapy increase or decrease?
- Are some of side-effects related to current therapy eliminated by antioxidants?
- Does antioxidant supplementation affect survival rates?

In accordance with these questions, lots of experimental and clinical studies were carried out to prove the role of antioxidants in cancer therapy [16, 24–30]. Results obtained from these studies were variable. This variation is basically related to cancer type and cancer grade. ROS-cancer relationship and antioxidant junction points are described **Figure 1**.

An antioxidant-cancer relationship is deeply discussed next part in terms of glioma.

4. Antioxidants and gliomas relationship

Gliomas are a class of primary central nervous system tumors and they originated from glial cells [1]. Glial progenitor cells have different subtypes: astrocyte, oligodendrocyte, and ependyma. In general, the classification of gliomas is based on these cell types [4]. The most detailed classification belongs to WHO. WHO suggests that four different grades (I–II–III–IV) are described for gliomas according to morphological and histological features [1]. Besides these features, some molecular and genetic features (epidermal growth factor upregulation, isocitrate dehydrogenase 1/2 mutations, p53 mutations, etc.) also alter the grading [2].

Tumor grade and class are major factors to determine the therapy options. Surgery, chemotherapy, and radiotherapy are preferred to treat the gliomas. After surgery, chemotherapy or radiotherapy is applied. For the glioma treatment, the most frequently encountered problems are the blood-brain barrier and drug resistance [31]. The blood-brain barrier is a control mechanism in relation to the transition of ions, molecules, and cells between the blood and brain. If a drug does not pass through the blood-brain barrier, it cannot reach the brain cells [32].

The second problem is drug resistance [33]. Temozolomide is the most common chemotherapeutic agent for gliomas. It is an alkylating agent [34]. In case of elevated levels of O^6-metil guanine DNA methyltransferase expression, temozolomide meets with resistance [35]. On the other hand, increased levels of antioxidant response system SLC7A11 triggered the drug resistance [31].

Over the past decades, antioxidant supplementation becomes a necessity for cancer treatment. Basically, antioxidants use to eliminate the elevated levels of ROS, but cancer in question nothing is understandable. For this reason, researchers have carried out some studies. Understanding the beneficial or harmful roles of antioxidants in cancer treatment is essential. Further to that understanding of ROS effects in terms of cancer progression is really important. ROS is a reason

for cancer progression, but in course of cancer development increased levels of ROS might be a cell-death option. Moreover, increased levels of ROS alter the cell signaling in cancer cell in consequence of acting as secondary messengers [17]. For instance, Akt overexpression is frequently showed in gliomas, and protein kinase C (PKC) activation stimulates some molecules like Akt, MAPK. All these molecules are under the control by cellular redox state [36]. As a result of these features, ROS antioxidants can be provided new approaches in order to treat glioma. It is still an unknown and questionable area for the researchers.

Accumulating data suggest two different approaches regarding antioxidant consumption. One is that antioxidants make tumor cells resistance against chemotherapy or radiotherapy and the survival rates are decreased. On the other hand, the second is that antioxidants protect the normal cells from oxidative damage and they are decreased side effects of therapy and provide better survival [8, 37, 38]. The next part of this chapter is related to evidence regarding these two opinions.

4.1. Evidence-based studies

Gliomagenesis is still an unknown, incurable, and lethal process. New and effective treatment strategies are the necessity and understanding the gliomagenesis is essential in order to develop these options. Experimental evidence indicates that antioxidants are sometimes friend, and in some cases, they are the foe.

4.1.1. In vitro studies

In 1995, Zhu et al. carried out a study to clarify the effects of selenium on rat and human glioblastoma multiforme cell lines. They used sodium selenite and showed that selenium had anti-proliferative effects on both A172 human glioblastoma cells and C6 rat glioblastoma cells, but it was more effective on human glioblastoma cells [39].

In 1997, Vartak et al. showed that some polyunsaturated fatty acids: gamma-linoleic acid (GLA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) supplementations increased the radiosensitivity and also radiation response on 36B10 rat astrocytoma cells [40].

In 1998, Vartak et al. compared the effects of GLA and linoleic acid (LA) on 36B10 malignant rat astrocytoma and normal rat astrocytes. They found that GLA was cytotoxic for astrocytoma cells, but not astrocytes. LA was not effective for both cells. It suggested that GLA might be used for astrocytoma treatment [41].

In 1999, Arora-Kuruganti et al. examined roles of oxidant (H_2O_2) and antioxidant (N-acetylcysteine, NAC) on U373-MG astrocytoma cell line. They observed that tumor cell proliferation was inhibited by NAC. NAC also induced H_2O_2 [25].

In the beginning 2000s, the first study came from Rooprai et al. They checked some anti-invasive and anti-proliferative agents: swainsonine, captopril, tangeretin, and nobiletin on four different glioma cell lines: ependymoma, oligoastrocytoma, anaplastic astrocytoma, and glioblastoma multiforme. Firstly, they observed that each cell line showed difference response

against agents. They found that the most effective agent was nobiletin on four different cell lines and it was decreased the MMP-2 and -9 secretions [42].

In 2001, Naidu et al. studied the effects of ascorbyl stearate (Asc-S) on human glioblastoma multiforme cells. They used different doses of Asc-S on T98G human glioblastoma cell lines for 24 h. They showed that Asc-S inhibited insulin-like growth factor-dependent cell proliferation in a dose-dependent manner. Asc-S modulated IGF-R expression, in consequence of this situation programmed cell death was triggered on T98G cells by Asc-S [43].

In 2007, Rooprai et al. studied on IPSB-18 human astrocytoma cells. They treated cells with selenite and found that selenite was altered the expressions of matrix metalloproteinases and their inhibitors. It was also decreased the epidermal growth factor (EGFR) expression. This was suggested that selenite had anti-metastatic effects [44].

In 2013, Pozsgai et al. studied on quercetin effects on glioblastoma standard treatment. They found that combination treatment provided significant reduction in cell viability in U251 and DBTRG-05MG glioblastoma multiforme cell lines. They also showed that quercetin alone, or in a combination with IR triggered the apoptosis [29]. In 2016, Lou et al. found that quercetin nanoparticles stimulated the autophagy and apoptosis by activating AKT/erk/caspase 3 signaling pathway [45].

In 2017, increasing cell proliferation of glioblastoma multiforme cell lines with low doses of selenomethionine was showed by Harmanci et al. [46].

The combination of berbamine and paclitaxel were decreased the cell proliferation on U87 glioblastoma multiforme cells [47].

Higher levels of ascorbate led the DNA strand breakages by creating genotoxic and metabolic stress on glioma cells, but it also caused the development of radioresistance [48].

4.1.2. Animal studies

In 1981, Newell et al. used a mixture of vitamins C and B12 in high dose on rats with glioma. They observed no difference in survival time between experimental and control groups [49].

In 1989, Wang et al. showed that retinoids (retinal, retinoic acid, retinyl acetate, and retinyl palmitate) and carotenoids (beta-carotene, lycopene, and crocetin) inhibited the tumor growth in C6 glioma cells inoculated rats [50].

A study regarding naringenin using was carried out on rats by Sabarinathan et al. [30]. With supplementation of naringenin in glioma induced rats the status of lipid peroxidation was decreased, on the contrary antioxidant status increased. Besides this, naringenin also modulate the glial-tumor cell proliferation [30].

In 2013, Perez de la Ossa et al. examined that Δ^9-tetrahidrocannabinol (THC) and cannabidiol (CBD) effects on tumor growth in xenograft glioblastoma multiforme model. THC and CBD loaded on microparticles and delivered locally. At the end of the study they found that THC and CBD stimulated apoptosis and induced cell proliferation and angiogenesis [51].

In 2013, Hervouet et al. found that using SUVIMAX-like diet (supplementation en vitamins et minéraux antioxydants), which was enriched with beta carotene, alpha tocopherol, vitamin C, zinc, and sodium selenite, was delayed the clinical signs on ethyl-nitrosourea induced glioma rat model, but gliomagenesis occurred. This diet just decreased the tumor aggressiveness [52].

In 2017, prolonged survival time was showed treatment with coptis chinensis on glioma induced mice model by Li et al. [53].

Combination of berbamine and paxitaxel was delayed the development of tumor U87 xenograft model [47].

4.1.3. Clinical trials

In 1990, Philipov et al. carried out a limited clinical study with 15 patients with malignant brain tumors. There was no significant survival prolongation with selenium addition on patients' diet [28].

In 1996, Lissoni et al. evaluated the effects of melatonin using with radiotherapy on 30 patients with glioblastoma multiforme. They showed that the melatonin addition in normal therapy provided prolonged survival time, decreased side-effects. Based on these results they suggested that concomitant therapy may be more effective for glioblastoma patients [27].

In 2010, Delorenze et al. exhibited that the relationship between daily intake of antioxidants and survival rate was variable depends on tumor grade. They also showed that the supplementation of higher dose vitamin E has increased the survival in grade III gliomas; otherwise, vitamin C and genistein were decreased the survival rate [26].

In 2010, the side-effects welding from radiotherapy were decreased with lycopene supplementation in patients with high-grade glioma [54].

In 2015, Mulpur et al. carried out a study to check complementary therapy options among glioblastoma multiforme patients. They found that multivitamins or omega-3-fatty acids did not affect survival, but for Vitamin D and E further investigations are necessity [55].

5. Conclusions

Cancer is a personal disease, for this reason, it needs special attention. The above-mentioned evidences have shown that antioxidant supplementation cannot safe at times. Researchers advocate two different opinions regarding using antioxidant in course of cancer treatment. The first opinion is traditional approach. It says antioxidants prevent the normal cell from oxidative damage and they induce toxicity and provide better survival rates. The second one shows the dark side of antioxidants. According to the second opinion: antioxidants are decreased the survival rates by triggering drug-resistance. When we consider these two opinions we can easily understand the requirement of this area.

The most urgent thing is clinical trials with larger sample size and long-term following. Evidence obtained from in vitro or in vivo studies cannot representative for the 3D organism. The effects

of antioxidant supplementation can determine appropriate clinical trials. Antioxidants' interference in chemotherapeutic mechanisms is still unknown and clinical fails of therapeutic approaches regarding redox modulation are obvious.

In summary, antioxidant cancer therapy remains incapable. ROS scavengers must give place to antioxidant inhibitors. ROS-related cell death mechanism is a novel approach to provide the selective cell death. Further investigations will need to see the effectiveness of pro-oxidant cancer therapy.

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