Chapter 1

The Potential Use of Plant-Derived Compounds in Glioblastoma Management

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Abstract

Glioblastoma or glioblastoma multiform (GBM), is recognized as the most frequent and malignant nervous system tumor. Conventional therapeutic strategies, such as surgical resection and chemo-radiotherapy, have done very little in prolonging the survival time of GBM patients. The difficulties in human GBM therapy are due to the inherently complicated pathological characteristic and numerous drug-resistance mechanisms. For this reason, more efficient therapeutic approaches are required for enhancing the treatment effect. One of the most attractive cancer therapy methods to date is the induction of tumor cell death by naturally occurring phytochemicals. In this chapter, we mainly summarize the most up-to-date findings regarding the representative plant-derived compounds that play important roles in the GBM treatment. Additionally, the applicability of phytochemical-loaded nanoparticles (NPs) as drug delivery systems (DDS) should also be closely considered and further investigated.

Keywords

Glioblastoma; Cancer therapy; Plant-derived compounds; Drug delivery systems

Introduction

Glioblastoma or glioblastoma multiform (GBM), a WHO grade IV glioma, is the most frequent and malignant nervous system tumor, and represents about 45% of all gliomas. Every year, approximately 9,000 newly-diag-
nosed cases are found in the United States alone. The current standard treatment for primary GBM is the maximal safe surgical resection, followed by radiation therapy with concurrent and adjuvant chemotherapy. Though these strategies and other medical advances in the treatment of GBM, the five-year survival rate is barely 0.05-4.7% [1,2]. The probably reasons for high mortality rate of GBM are as follows: With self-renew and heterogeneous neoplastic subpopulations, GBM have the ability of aggressive proliferation and highly invasive. As GBM could diffusely infiltrate the surrounding brain tissue, leading to incomplete surgical excision, the patients diagnosed with GBM often have a poor prognosis. The blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB) are the main hampers to prevent some macromolecular substance entering the cerebral circulation, resulting in the failure of both conventional and targeted therapies in the treatment of glioma [3,4].

Over the last ten years, two chemotherapeutic alkylating agents, carmustine (BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea) and temozolomide (TMZ), have been approved by the U.S. Food and Drug Administration for treating malignant gliomas [5,6]. However, GBM often reacts poorly and exhibits resistance to conventional available chemotherapeutic approaches, with some inherent cellular mechanisms, including drug delivery, cancer stem cells (CSC), autophagy, and miRNAs [7,8]. In these conditions, it is essential to develop more efficient therapeutic approaches to limit occurrence and/or aggressiveness of this tumor.

Figure 1: The probable anti-tumor mechanisms of plant-derived compounds on gliomas.

Natural compounds or phytochemicals, are increasingly being exploited by researchers as promising bioresources for developing anti-cancer drugs, because they have the potent tumor-killing action and are relatively nontoxic to healthy cells [9] (Figure 1). For example, sili- binin, a natural plant component of milk thistle seeds, has been shown to enhance the cytotoxic efficacy of TMZ in TMZ-resistant LN229 glioma cell lines [10]. And triptolide, isolated from the traditional Chinese herb Tripterygium wilfordii, could caused a dose-dependent decrease in proliferation and increase in apoptosis in the

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glioma U87 and U251 cell lines via a p53-independent pathway [11]. Salvianolic acid B (SalB), the main water-soluble bioactive compound extracted from the Chinese medical herb Danshen, could significantly inhibit cell proliferation and induce apoptotic cell death in glioma U87 cells [12]. Based on these findings, the potential of plant-derived therapeutics should be closely considered and further investigated, to become a new frontier for research into GBM treatment.

**Natural Compounds on miRNA Regulation**

miRNAs, one key component of the non-coding RNA family, are single-stranded molecules that modify the transcription of target gene at the post-transcriptional level. As proper controlling of miRNA expression is required for maintaining physiological cell homeostasis, deregulation in miRNAs expression could contribute to the different biological processes of various cancers, including the cancer initiation, progression, metastasis, and drug resistance [13]. Recently, studies have indicated that miRNAs are appealing potential biomarkers and therapeutic targets of GBMs, and altering the miRNAs expression by bioactive compounds could be a promising strategy for GBM therapy [14,15]. Tezcan et al. found that Ficus carica atex (FCL) could synergistically enhance the therapeutic effect of TMZ on GBM tumors. In addition, with less cytotoxic activity in non-tumor cells, FCL also induce the obvious anti-invasion effect by up-regulating Let-7d expression in human GBM cells [16]. Similarly, the findings from Tunca group have demonstrated that Olea europaea leaf extract (OLE) could change the miRNA expression profiles in T98G cells. OLE could specifically up-regulate the expression of miR-181b, miR-153, miR-145, miR-137 and Let-7d, which are involved in the cell cycle and apoptotic pathways. This altered expression pattern of miRNAs induced by OLE has been correlated with the therapeutic response to TMZ in GBM tumors [17]. Moreover, OLE could interfere with the pluripotency of glioblastoma stem cells (GSCs) by modulating miRNA expression, furtherly causing cancer cell death with different TMZ responses [18]. Even though further studies and validations are needed to be done in vivo, these results confirm the excellent anti-tumor effect of miRNAs modulation by plant-derived compounds, which would pave a novel way for the treatment of GBM.

**Natural Compounds on Autophagy Regulation**

Autophagy is an evolutionarily conserved biological process and links to several cellular pathways in normal organisms. It can maintain cellular homeostasis by eliminating the damaged organelles and misfolded proteins,
which are deleterious to cellular survival [19]. However, it also plays an important role in multiple cancer processes, including cancer development, progression and therapy [20].

Recently, studies have indicated that autophagy is frequently activated in tumor cells by radiation or chemotherapeutic drugs, and this process represents a potential target for GBM therapy [21]. Moreover, in most cases, autophagy is a pro-survival mechanism in cancer cells under therapeutic stress, and induction of autophagy is associated with therapy resistance [22]. Therefore, inhibition of autophagy by bioactive phytochemicals would promote the response of tumor cells to cancer therapeutic agents. Thymoquinone (TQ), a bioactive component derived from the plant Nigella sativa, could induce the DNA damage and glioma cell death dependent on the cellular DNA-PKcs status, with selective cytotoxicity for cancer cells compared to normal cells [23]. Further study conclusively showed that TQ functions as an autophagy inhibitor, and results in the perturbation of the lysosomal membrane and a leakage of lysosomal protease cathepsin B (CTSB) into the cytosol, finally provoking the caspase-independent cell death [24]. Another anti-neoplastic compound, which recently draw the attention of scientists, is Resveratrol (3,5,4’-trihydroxystilbene, Rsv), the polyphenol component extracted from grape skin, red wine and nuts. With minimal toxicity and side-effect, Rsv functions as a potent anti-oxidant, which can scavenge the oxygen radical in order to promote the normal cells survive. Moreover, Rsv has the ability to cross the BBB, supporting its potential as a therapeutic agent in human gliomas [25]. Lin et al. suggested that Rsv could effectively inhibit the TMZ-induced cytoprotective autophagy and subsequently induce malignant glioma cell apoptosis in vitro and in vivo [26]. Under combined treatment of Rsv and TMZ, glioma cell lines display a stable senescence phenotype characterized by a higher rate of G2/M-phase arrest, which can improve the long-term outcomes of TMZ on GBM [27].

Natural Compounds as Anti-Oxidant

The brain tissue appears especially strong sensitivity to the oxidative stress, because of its high rate of blood flow and oxygen consumption. Indeed, compared with normal cells, tumor cells present high accumulation of oxidative damage to biological macromolecules [28]. Even so, it is well known that aging-associated diseases, including cancer, are triggered by oxidative damage markers, suggesting that a high level of oxidative stress, like the excessive reactive oxygen species or free radicals production, can stimulate the cancer cell survive [29]. Various intracellular signaling pathways that mediate pathological processes, including Ca2+ and calmodulin-dependent protein kinase II (CaMKII), mitogen-activated protein kinases (MAPKs), or phosphoinositide 3-kinase (PI3K), could be activated by ROS [30,31].
Since the brain is characterized by a high rate of oxygen consumption, most of the phytochemicals, like shikonin, a quinone-based natural product from the root of *Lithospermum erythrorhizon*, can modulate the level of oxidant stress, which can interfere with the progression of malignant gliomas [32]. Pouliquen et al. have studied the influence of experimental diet, containing various phytochemicals with anti-oxidant properties, on the incidence of gliomas. This phytochemical-enriched diet has the systemic effects on the prevention of brain tumor development by decreasing the genes involved in the oxidative stress, such as superoxide dismutase (SOD-1 and SOD-2) [33]. Meanwhile, a SUVIMAX-like diet (Supplementation en Multivitamines et Minéraux Antioxydants) could reduce the Mn-SOD mRNA expression, one key regulator of oxidative stress, leading to significant inhibition of cell growth in glioma [34]. A randomized double-blind trial was designed to furtherly make sure that SUVIMAX-like diet could decrease the cancer incidence at nutritional doses [35]. In addition, Chang et al. found that γ-mangostin, isolated and purified from the hull of the tropical fruit *Garcinia mangostana*, could induce the cytotoxicity of GBM cells through promoting intracellular ROS productions and mitochondrial dysfunction. And compared with vitamin E, one of the most powerful anti-oxidants, γ-mangostin shows much stronger antioxidant activity [36]. The γ-mangostin derivative, garcinone B, could both inhibit prostaglandin E2 (PGE2) release and nuclear transcription factor-κB (NF-κB) -mediated inflammation-associated genes transcription in C6 rat glioma cells [37]. Above all, these observations tend to confirm that phytochemicals with antioxidant properties can play a prevention role to limit the progression of GBM, functioning as a neuropharmacological tool.

**Natural Compounds on Inflammation Regulation**

Inflammation is a very common and important basic process, participating in regulating physiological and pathologic processes. Under physiological conditions, in response to tissue injury, larger cytokine responses to stressors and pathogens are provoked to initiate and maintain inflammatory responses [38]. However, abnormal inflammatory responses can lead to negative mental and physical health consequences, including aging and cancer [39,40]. Particularly, the tumor microenvironment, which is largely stimulated by inflammatory cells, is an indispensable participant in the neoplastic process, enhancing invasion, angiogenesis, extracellular matrix remodeling and targeting therapy [41].

Given that the inflammatory microenvironment affects host immune surveillance and therapeutic response, anti-inflammatory strategies have been envisioned to reduce the risk of developing glioblastoma [42]. Naturally derived anti-inflammatory compound, corosolic acid, sig-
significantly inhibits the expression of CD163, one marker of cancer inflammation-related M2 macrophages, and induces caspase-dependent cell apoptosis in GBM cells [43]. A common flavonoid in many types of plants, luteolin, could both depress interleukin-1β (IL-1β) triggered inflammation biomarker cyclooxygenase-2 (COX2) expression and inhibit IL-1β-mediated phosphorylation of protein kinase B (Akt/PKB) and NF-κB [44]. Moreover, Lamy et al. reported a biphasic effect of luteolin on the GBM treatment, which induced anti-inflammatory and pro-apoptotic characteristics at low (≤15μM) and high (>15μM) concentrations, respectively [45].

**Targeting Metastasis by Natural Compounds**

Tumor metastasis, involving in various complex and dynamic processes, often leads to poor quality of life and inevitable death in cancer patients. During the migratory process, signaling pathways that regulate the extracellular matrix and tumor cell invasion have been reported to be influenced by the natural products and their active components [46]. Therefore, studies on therapeutic compounds to anti-metastasis are one of the major directions to fight cancer in nowdays. Natural nutrient mixture, mainly composed of amino acid and green tea extract, could completely inhibit the invasion of glioma cell lines by prevent the secretion and expression of matrix metallo-proteinase-2 (MMP-2) [47]. In the traditional Indian medicine system, *ashwagandha* is one of the most versatile and safe plants. Kataria et al. found that the water-solution extract of *ashwagandha* leaves (ASH-WEX) could inhibit the glioma cell migratory by up-regulating neural cell adhesion molecule (NCAM), which is generally regarded as the cell-cell interaction molecular and associated negatively with cellular motility [48]. *In vitro* and *in vivo* studies have indicated that low doses of these water extracts could present the neuro-protective activities against oxidative stress [49]. Thiyagarajan et al. screened a novel and specific inhibitors, 16-hydroxy-cleroda-3,13-dien-16,15-olide (HCD), of focal adhesion kinase (FAK), which plays an important role in cell migration. They found HCD could inhibit the activity of MMP-2 and MMP-9, and modulate the expression of epithelial mesenchymal transition (EMT) proteins, further to block the metastasis of GBM cells [50]. Another phytochemical, Honokiol, present in *Magnolia officinalis*, have an intriguing anti-invasion effect on the T98G cell lines, with the ability to cross the barrier BBB and BCSFB [51]. Taken together, these findings prove that plant-derived compounds could be beneficial for chemoprevention on cancer invasion and metastasis.

**Drug Delivery Systems**

As for all plant-derived compounds, transport is an important issue, which should be paid much more attention in the future assays. Drug delivery systems (DDSs) can be used to solve the problems and questions about
the actual bioavailability, metabolic process and toxicity. Several seminal studies have ensured that certain delivery systems, like the nanoparticles (NPs), can efficiently load the phytochemicals and transfect them into the targeted GBM tumor cells without clear side effects [52-54]. Using copper-substituted mesoporous silica nanoparticles (MSNs), a novel HCD-loaded NPs delivery system was designed, and meanwhile, the outer surfaces of MSNs-HCD were further coated with enteric polymers to prevent the drug from exposing to the stomach acid when oral administration. With a sustained release profile and no obvious toxicity, this enteric-coated MSNs-HCD could inhibit tumor growth and trigger apoptosis by increasing the mitochondrial dysfunction and intracellular ROS production in C6 glioma cell lines and xenograft glioma model [55]. Mohanty et al. synthesized Rsv stabilized gold nanoparticles (R-GNPs), whose surface were loaded with doxorubicin, and found that doxorubicin-R-GNPs could easily deliver the drug through the cell membrane and significantly enhance the cytotoxic activity of Rsv on human glioma carcinoma cell lines. These R-GNPs show excellent biocompatibility and stability in the physiological pH [56]. The third nanoparticles system is dendrosome, which encapsulated curcumin in a nontoxic nanocarrier. Free curcumin, from turmeric, shows the anti-cancer activity on rat C6 glioma cells, but the low bioavailability and water solubility limit its further use in vivo experiments and clinical trials [57]. However, dendrosomal curcumin could overcome the main disadvantages of free curcumin, and strengthen the specific toxicity effect on cancer cells [58]. These results indicate that with more suitable drug delivery systems developed by nanotechnology, the anti-glioma effects of phytochemicals would be further increased, and these towardly bioresources could be stimulated to apply into new subject areas.

Conclusion and Remarks

In the last decade, bioactive plant-derived compounds have been regarded as antineoplastic compounds for the treatment of many cancers, including gliomas. However, their biological effects are easily influenced by many factors, such as the stability and the delivery strategy. A better understanding of the real efficacy and mechanisms of these compounds, particularly in human patients, represents a matter of great interest for possible clinical application in future. As the standard chemotherapy drugs currently used to GBM therapy are BCNU and TMZ [6, 59], more researches are required to evaluate the efficacy and synergistic effects of combination natural products with BCNU or TMZ. In addition, some other directions are also needed to pay close attention. As cancer chemotherapy drugs, the off-target effects on normal tissues should be principally concerned [60]. Chemical structure modification or new activated compounds extraction would be employed to target tumor cells more selectively with minimal side effects on normal cells. Because the bio-
availability have a key effect on the biological properties of compounds [61], it is essential to emphasize this point before further discussing the tumoricidal potentials. And the strategies to improve the bioefficacy, including the drug-carrier systems, are warranted. The barrier BBB and the BCSFB, which are composed of capillary endothelial cells connected by tight junctions, could restrict the availability of anti-tumor compounds. Development of drug delivery systems can enhance the permeability of agents into the targeted GBM cells [62]. Most of the reported natural phyto-reagents in cancer-prevention are water insoluble. Thus extensive works should focus on the technologies to improve water-soluble, such as solvent exchange method, to make sure the natural hydrophobic compounds served as potentially safe glioma-therapeutic drugs [63]. So far, as the high-throughput screening (HTS) could offer the advantages of speed, cost-effectiveness, genome coverage, and immediate biological relevance, some HTS technologies have been used to identify new bioactive natural components for drug development. For instance, Park et al. performed a HTS system, based on the homogeneous time-resolved fluorescence (HTRF) technology, to discover selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) from a chemical library [64]. Using partial purification approach, a novel collection method, Henrich et al. screened three active natural product extracts, which could inhibit the growth of NF1 astrocytoma cell with no effect on the normal astrocytes [65].

Natural compounds are now playing an attractive role for the development of tumor treatment and prevention strategies. New discoveries about active compounds have enhanced our knowledge of plants and herbs. What then is the future of plant-derived compounds? It probably lies in filling a niche for the glioblastomas, whether primary or recurrent, for which there is no most effective and radical treatment. Specifically, increasing the synergistic effect of phytochemical and current standard chemotherapeutics might result in the better survival rate in patients with gliomas. In view of the crucial role in gliomas therapy, natural molecules, with striking anti-tumor ability in vitro and in vivo, should enter clinical trials as soon as possible to evaluate the safety and efficacy in GBM patients. Moreover, development of the delivery modalities seems very important for the reagents administration, which could decrease the side effects.

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