Chapter

New Approaches in the Treatment of Glioblastoma Multiforme

Lee Roy Morgan, Branko Jursic, Marcus Ware and Roy S. Weiner

Abstract

Central nervous system (CNS) malignancies are rare, but commonly fatal and glioblastoma (GBM) is the most common of the primary brain tumors. In contrast to metastatic malignancies involving the CNS, which have external blood supplies that develop when the malignant cells penetrate the blood-brain-barrier (BBB), GBM generates its own intracerebral neovascular support system. Thus, the therapeutic issues as discussed herein review the development of drugs and therapeutics that will penetrate the BBB and are cytotoxic *to* GBM and other brain tumors. Since GBM is a CNS malignancy with minimal effective therapeutic options available, designing drugs and therapeutics as treatment for this malignancy that penetrate, but do not disrupt the BBB is the goal of this chapter. 4-Demethylcholesteryl-4-penclomedine (DM-CHOC-PEN) was designed and developed because of its lipophilic properties that *would* potentiate crossing the BBB and penetrate brain tumors. The drug has now completed Phase I/II clinical trial in humans with primary brain malignancies *demonstrating* objective responses in GBM. In addition, preliminary experiences with naturally occurring polyphenols—curcumin, quercetin, catechins and phloretin and derivatives—are reviewed as potential naturally occurring anti-glioblastoma agents.

Keywords: temozolamide (TMZ), glioblastoma multiforme (GBM), recurrence, radiosurgery, chemotherapy, 4 demethyl-4-cholesteryloxycarbonylpenclomedine, DM-CHOC-PEN, and multimodality treatment

1. Introduction

Approximately 48% of all primary malignant brain tumors are glioblastoma multiforme (GBM), and more than 10,000 people will succumb to the disease in the US each year alone (1). The 5-year relative survival rate for these patients with GBM increased only from 23%, as reported in the mid-1970s, to 36% in the early 2000s [1, 2]. Adding to the complexity of the disease is the cancer's ability to rapidly mutate, so even in different locations in the brain of the same patient, GBMs encompass a mosaic of cancer cell types, posing a major challenge for tumor-targeted therapy [3]. Thus, despite the advancements in the management and treatments for malignancies which we review here, the prognosis for long term survival for glioblastoma (GBM) continue to be dismal [4].

2. History of the disease

For metastatic cancers involving the brain there are cancer-associated-breaks and related neovascular channels in the BBB that allow drug penetration [4]. However, GBMs commonly lack facilitating neovascular changes in the BBB and must rely on drug lipophilicity and/or target transport mechanisms for anti-cancer agents to penetrate the BBB. GBM responses to the present therapies available are dismal and new therapies that penetrate the BBB are needed. Classically GBMs induce their own intracerebral neovascular blood supply within the brain that supplies the tumor mass with blood and nutrients—no extra-BBB blood supplies are involved; thus, the principle issue is penetrating the BBB [2, 5].

The major goal of this article is to initiate new ideas in the management of GBM, as well as other types of CNS malignancy. The core therapeutic challenge is to obtain long term objective responses through mechanisms involving drug penetration of the brain *via* the BBB and utilizing the changes in the chemistry of GBM malignancies.

In the treatment of GBMs, for drug and therapy modalities to be effective, there must be small/diffuse vascular accesses/openings or breaks (surgery sites), or lipophilic target pathways through the BBB secondary to interactions with a receptor or transport mechanism for penetration of the brain and CNS tumor masses [6].

Needless to mention, many treatment approaches that should be useful therapies for GBM also possess toxicities secondary to particle size and/or interaction with inappropriate sites—locally or distant—and unable to reach the tumor masses, and are not employed.

GBM has not been associated with smoking or any other lethal factors. The tumor remains the most common and lethal form of CNS brain cancers and one of the most difficult to manage.

In summary, since GBMs do not induce neoplastic blood support systems, drug and immune tumor targets, immune therapies do not easily penetrate the BBB and GBMs have not responded well to systemic therapies and new therapies should be aggressively evaluated [1, 2, 7, 8].

3. Current drug therapies

The O^6-methylguanine-DNA-methyltransferase (MGMT) gene encodes for an important DNA repair protein which acts by removing alkyl products from the O^6 position on guanine. A so-called "suicide enzyme," following removal of the alkyl groups, the newly alkylated MGMT protein, is then marked for degradation by ubiquitination [8]. Proper functioning of the gene is important for maintaining cell integrity. Epigenetic silencing of the MGMT gene by methylation of the CpG islands of the promoter region has been shown to correlate with loss of gene transcription and protein expression [9, 10]. Loss of expression of the MGMT protein results in decreased DNA repair and retention of alkyl groups, thereby allowing alkylating agents such as carmustine (BCNU), lomustine (CCNU), and temozolomide to have greater efficacy in patients whose tumors exhibit hypermethylation of the MGMT promoter, reducing the MGMT protein concentration [10–13].

3.1 Temozolamide

Temozolamide (Temadar, TMZ) (**Figure 1**) continues to be the standard therapy +/− radiation for GBMs. However, the benefit of the therapy has been less than

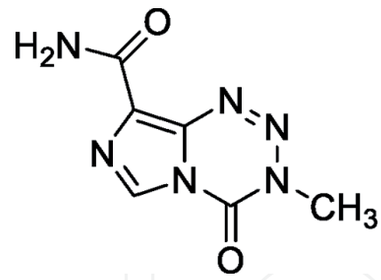


Figure 1.
Temozolamide (Temadar, TMZ).

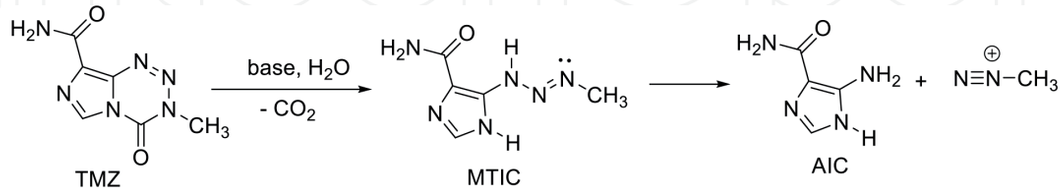


Figure 2.
Mechanism of action for TMZ.

desirable since methylated *MGMT*- GBMs are most sensitive, as well uncommon [11–13]. Once TMZ passes through the BBB its mechanism of action is as follows:

TMZ is quickly and almost completely absorbed from the gut, and readily penetrates the blood– brain barrier and brain. The concentration of drug in the cerebrospinal fluid is approximately 30% of the concentration in the blood plasma. Intake with food decreases maximal plasma concentrations by 33%. TMZ is a prodrug; it is hydrolyzed at physiological pH to 3-methyl-(triazen-1) imidazole-4-carboxamide (MTIC), which further splits into monomethyl hydrazine—likely the active methylating agent—and 5-aminoimidazole-4-carboxamide (AIC) [13].

TMZ also induces breaks in the BBB and transforms several tumor marker receptors [13]. The therapeutic benefit of temozolomide depends on its ability to alkylate/methylate DNA, which most often occurs at the N^7 or O^6 positions of guanine residues *via* the methyl hydrazine metabolite (**Figure 2**).

The time of day that the drug is administered may be of importance. Drug administered early in the AM appears to be more active than when administered in the evening. Since the drug is lipophilic and morning meals are commonly high in lipids may be a possible explanation.

4. Core therapeutic challenges to obtaining long term objective tumor responses

There are numerous challenges to be considered when designing new drugs as therapy for primary CNS malignancies.

- Transport of drugs through the BBB. Although the use of drugs and protocols that are designed to include tumor target markers is becoming popular, the penetration of the BBB is still an issue.

- For focal lesions, surgical resection followed by TMZ plus radiation is acceptable practice.

- The presence of the PD-1 surface antigen in some GBM tumors has proven that the presence of tumor target check point markers may have a role in combination therapy when present. The latter approach is of major interest for future trials.

- Developing new drugs that are small or have unique transport mechanisms

- Identifying surface receptors on the BBB that will assist with drug transport into the brain and GBMs.

- Taking advantage of the BBB's lipophilicity is still a viable option that must be considered in drug/therapeutic design.

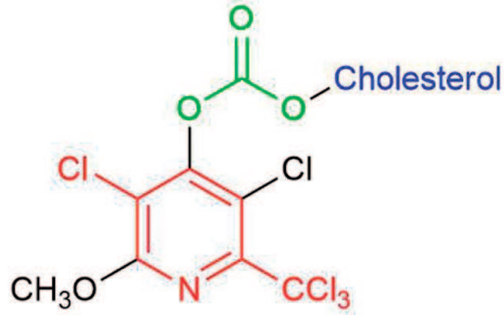
Due to the Warburg-associated inductive effects present, cancer cells utilize glucosamine in contrast to glucose in the Krebs cycle for energy [3, 4, 14]. Although breaks in the BBB similar to those seen in metastatic cancers involving the CNS are not observed in the brains with GBM present, microneovascular support is present in the GBM associated para-cerebral environment.

There are new reports regarding tumor-target marker agents that are demonstrating activity against target-negative GBMs, however, more new agents that do not require a tumor-target marker for activity are needed [1]. Drug design needs to take advantage of natural target mechanisms *via* the BBB [3].

In this chapter we discuss several interesting non-tumor target designed agents [2].

4.1 Designing agents to diffuse through the BBB

4-Demethylcholesteryl penclomedine (DM-CHOC-PEN) (**Figure 3**.) was designed and developed because of its lipophilic properties that was anticipated to potentiate crossing the BBB and penetrating brain tumors [3]. The basic nucleus penclomedine was developed at the NCI- Southern Research Institute as treatment for brain tumors, but was withdrawn from clinical trials because of CNS toxicities (seizures) [14, 15]. The cholesteryl ester was added to the penclomedine nucleus at DEKK-TEC (see below) to increase lipophilicity [1].



- Pyridine ring w/ bi-functional alkylating groups - a *bis*-alkylator – red
- Lipophilic cholesterol moiety - blue
- Carbonate - high energy linker – green
- Binds to DNA's cytosine/guanine nucleotides in DNA *via* replacements of chlorine groups at positions - 2 and 5.

Figure 3.
DM-CHOC-PEN and functional moieties. [3, 14–16].

4.2 DM-CHOC-PEN—Mechanism of action

During Phase I clinical pharmacodynamics studies when DM-CHOC-PEN was administrated IV, the drug was identified associated with erythrocytes (~50%), which is considered to be the mechanism by which it enters the cerebral circulation (**Figure 3**) and, therefore, available for transport into the tumor bed and the cancer cells resident therein [1, 4, 6]. The drug has been identified in intracranial metastatic NSCLC tissue [1,].

Glucosamine is a component of the mucopolysaccharides that involved in the chemistry of red blood cell (RBCs) surface membranes and DM-CHOC-PEN has an affinity for glucosamine (**Figure 4**) [4]. Association of DM-CHOC-PEN with

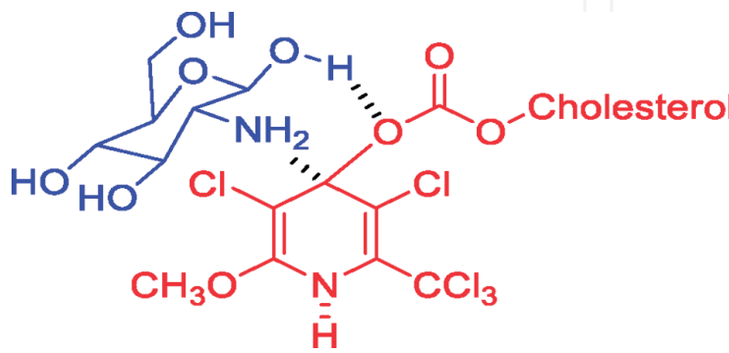


Figure 4.
DM-CHOC-PEN transport into CNS with glucosamine on RBC surfaces.

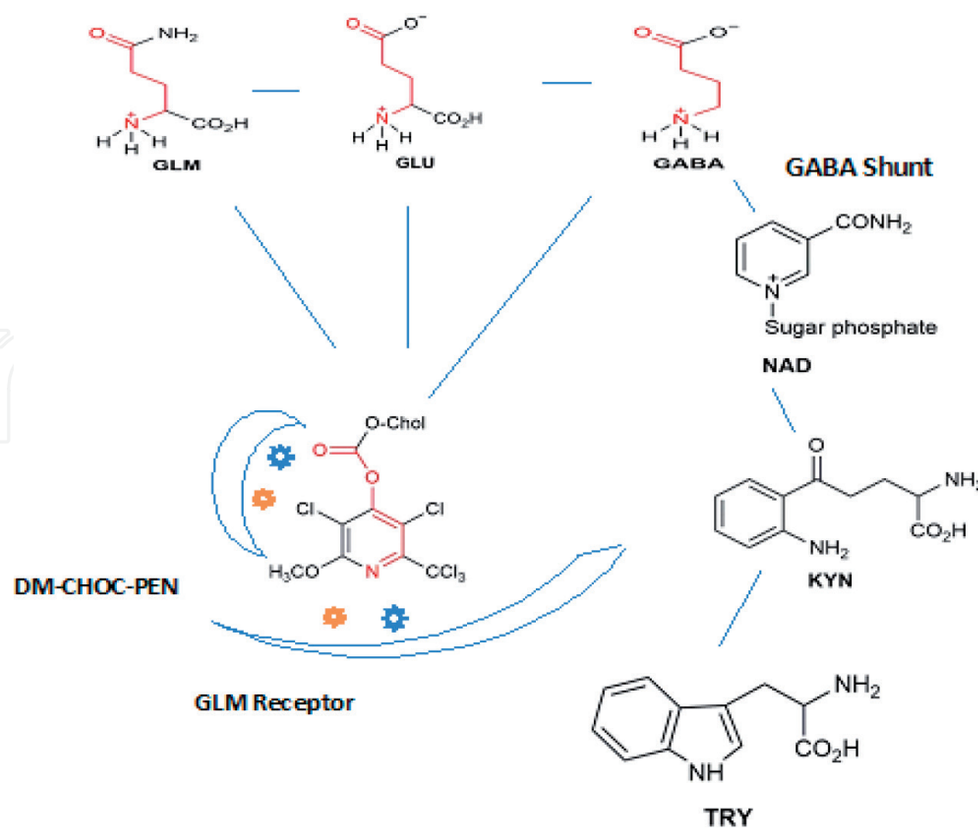


Figure 5.
DM-CHOC-PEN's transport into cells—Similarity with glutamine—Similarity with glutamine. NAD = pyridine nucleotides, KYN = kynurenine, and TRY = tryptophan.

glucosamine allows the drug to form complexes with the surface of RBCs and be transported into the brain (**Figure 4**).

After transportation through the BBB and into the brain, DM-CHOC-PEN is transported into cancer cells with glutamine because of similarities with that structure (**Figure 5**).

Figure 6 represents a possible complex between DM-CHOC-PEN and glutamine that can occur after the former penetrates through the BBB into the brain and transported into GBM cells. Cancer cells, especially GBM, utilize glutamine as a source of C & H for ATP synthesis [4]. The Warburg effect is present in the GBM cells, thus glucose is not utilized for ATP synthesis [4].

Figure 7 continues to be the best explanation of how DM-CHOC-PEN penetrates the BBB and intracerebral GBMs [2–6]. This mechanism was proposed by our group several years ago and continues to be a working model [2–6].

Table 1 reviews the results reported during Phase I/II clinical trial with DM-CHOC-PEN in primary brain tumors in adults [5, 17]. Unfortunately, as noted in **Table 1**, DM-CHOC-PEN is not active in all GBMs treated to date [5, 17].

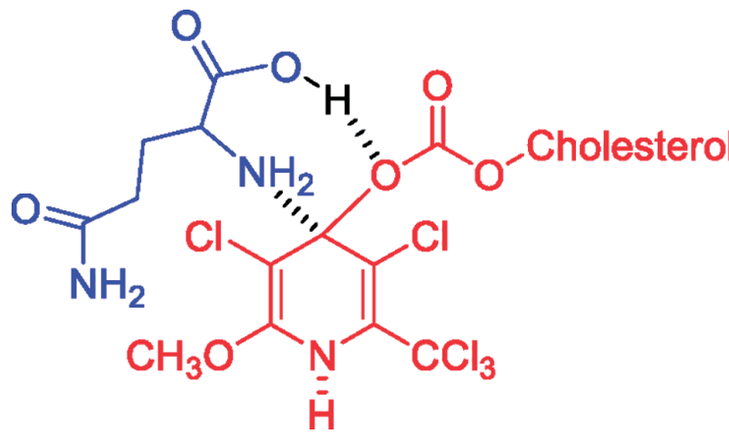


Figure 6.
Complex of DM-CHOC-PEN with glutamine.

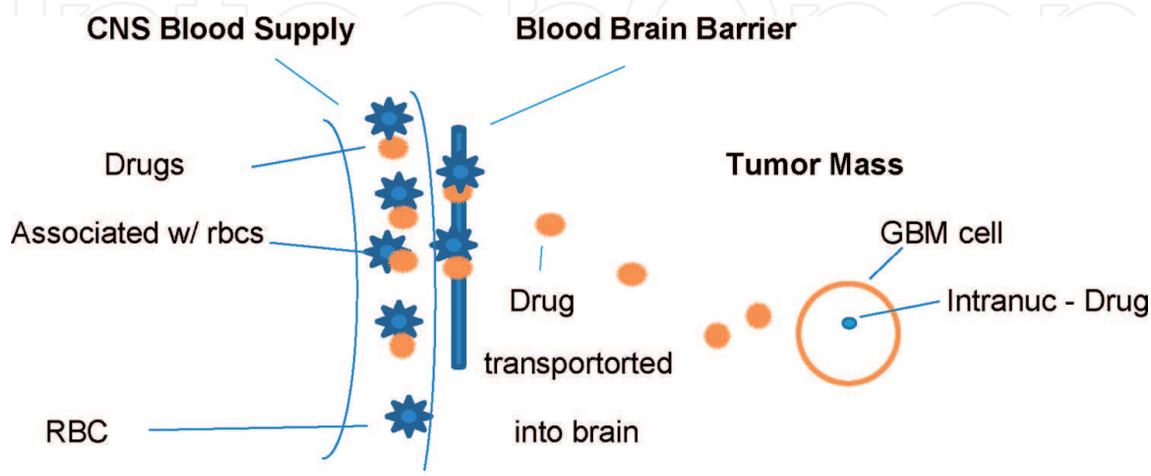


Figure 7.
Overview—Mechanism of action for DM-CHOC-PEN [2–6].

Cancer type	No. of subjects	DM-CHOC-PEN doses every 21 days (per kg)***	No. of responders (NED)	OS (OS ≥6 mo)
Glioblastoma*,**	11*,**	39, 85.8 or 98.7	2*,**	(6–13 mo.)*,**
Oligoastrocytoma*,**	2*,**	85.8 & 98.7	1**	3
Astrocytoma**	1**	85.8	1**	58 mo.

*Phase I.
**Phase II.
***Method of Treatment—DM-CHOC-PEN (mg/m^2) was infused IV over 4 hr. every 21 days to each patient—aged 37–78 y/o [5, 17]; NED—no evidence of disease [5, 17].

Table 1.
Primary brain tumor response to DM-CHOC-PEN therapy by cancer type-during phase I/II trials.

During the trials, tumor tissue from several patients that received the drug were obtained and analyzed. Adducts were identified that support the DNA sites that are alkylated by DM-CHOC- PEN and do not involve O^6-guanine sites, thus DM-CHOC-PEN should be active in most types of GBMs (**Figure 8**).

4.3 Immunotherapy targets

The principle challenge to the treatment of GBM, as exists for all tumors involving the CNS, is the difficulty to penetrate the blood brain barrier (BBB) and deliver drugs into the CNS and GBM [1]. In GBM, the BBB is weakened, allowing immune cells from the periphery to penetrate the CNS. However, GBM tends to selectively attract or turn immune cells that infiltrate the tumor into immune suppressive cells which lack anti-cancer activity [1].

Most immunotherapies target the reactivation of effector T-cells, which attack and eliminate cancer cells. But, in GBM, the effector T-cell infiltration is very low, secondary to the above inhibitory immune suppressive properties, and there is an abundance of immunosuppressive myeloid cells and a low concentration of cytotoxic cells [1]. Thus, developing immune modulators that prevent impairment of cytotoxic lymphocytes is of potential importance and could be useful alone or with cytotoxic agents [1].

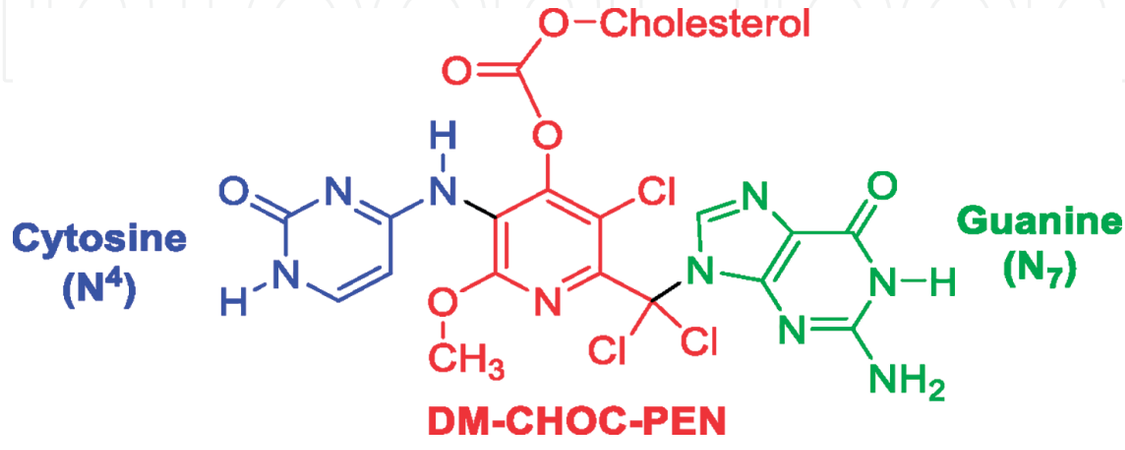


Figure 8.
An adduct has been identified in GBM tumor tissue obtained from patients post-DM-CHOC-PEN therapy.

4.4 Phenolic anti-glioblastoma compounds

Medical application of phenolic compounds is well documented through decades [18]. Current research trends are exploring the senotherapeutic activity of these agents [19–22]. The elevation of the presence of the senescent cells seems to be the central part of aging and age- related diseases including cancer [23]. There are increasing numbers of reports referring to the use of plant extracts that are phenolic compounds in ant-glioblastoma studies [24, 25].

Considering that targeted therapy for glioblastoma has had promising results *in vitro* monolayer cultures, the results from preclinical and clinical trials has been disappointing partly due to the poor blood brain barrier penetration. There currently is more emphasis on application of natural phenols that are able to penetrate the BBB as alternatives for glioblastoma treatment [26, 27].

Anti-glioblastoma activity has been investigated in depth for several phenols—curcumin, quercetin, catechins, and phloretin, to name a few [28–31]. In two-dimensional cell line tests, the above demonstrated that their IC50 values were ~ 50 μM concentration [32]. In addition, less than 2% of low molecular weight organic molecules crossed the BBB. For some phenolic compounds that cross the BBB a positive anti-cancer effect was observed [33]. However, the presence of phenolic compounds in the brain has been confirmed in only a few reports.

Figure 9 reviews natural phenols that have been extracted from plant purified and tested for anti-glioblastoma activity; majority of the phenols were glycosylated [34]. It has been well demonstrated that glycosylated organic compounds easily cross BBB [34, 35]. A perfect example of a glycosylated phenol that crosses the blood-brain barrier is curcumin oligosaccharide.

The IC50 value for curcumin after 24 hr. in a U87 cell culture was 10 μM and 13 μM for cultures with T98 cells [34]. However, in pre-clinical mice studies there was no detectable amount of curcumin in the brain or in T98 GBM cells after its intraperitoneal injection (IP). On the other hand, when curcumin gluco-oligosaccharide was injected I.V. to mice, 18 ng of curcumin per 1 g of brain tissue was determined. In addition, 5 days after the IP injection of the oligosaccharide into C57BL mice bearing intracerebral brain tumors, complete responses were observed [36].

This suggests that two-dimensional cell test results for anti-glioblastoma oligosaccharide conjugates can be translated to animal models. With this in mind phenolic

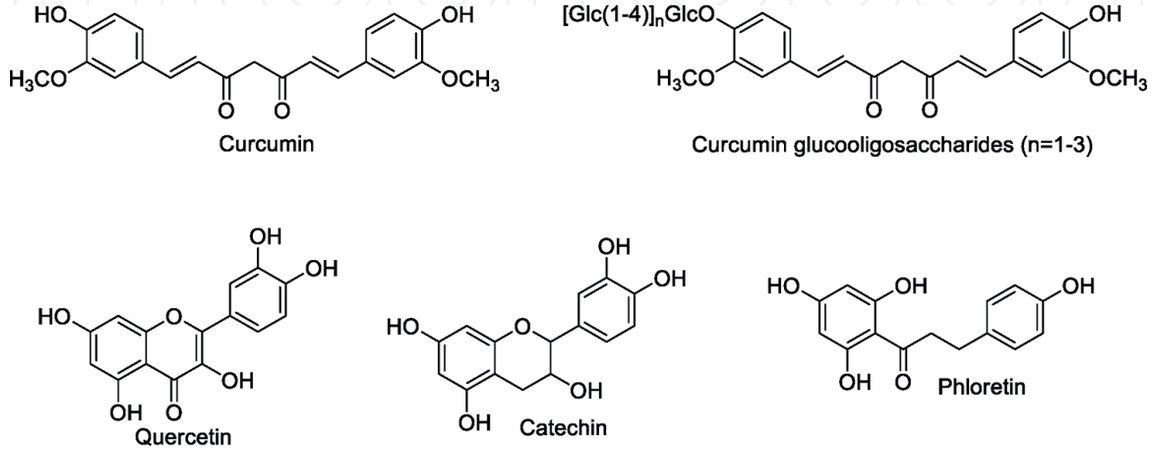
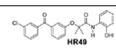
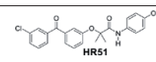
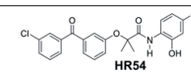


Figure 9.
Structures of naturally occurring anti-glioblastoma phenols.

Phenol			
CV	0 ± 0.27	1.1 ± 1.42	1.89 ± 1.56
VLR	1 (logP = 5.49)	1 (logP = 5.49	1 (logP = 6.09)
BBB_Score	2.24/6 (37%)	2.24/6 (37%)	2.38/6 (40%)
CNS_ MPO	3.14/6 (52%)	3.14/6 (52%)	2.90/6 (48%)

*GBM cell line LN229 growing in culture was employed as the test system. Test compounds were evaluated in the 100 nanomolar—100 μM conc. Ranges VLR = violations Lipinski's 5 rule; CV = Cell viability (% of control) mean ± SD at 25 μM; VLR = violations Lipinski's 5 rule; BBB Score = Blood-brain barrier score [38]; CNS-MPO = central nervous system—multiparameter optimization [39]. *Fenofibric acid (2 microgm/mL) was used as a standard and demonstrated no activity in culture.*

Table 2.
Comparison of cell (LN229) viability and compute brain penetration ability for fenofibric acid phenols HR49, HR51, and HR54.*

derivatives of fenofibric acid are being evaluated in clinical trials to document their activity as anti-GBM agents [37].

A number of phenolic fenofibric acid derivative were synthesized and tested against the glioblastoma LN229 cell lines. There were numerous fenofibric acid derivatives that had IC50 values between 1 and 10 μM (see below).

Several of the derivatives are listed in **Table 2**. According to computational studies, a majority of these compounds have high lipophilicity (logP >5), but their probability of crossing the BBB was below 50%. Studies *in vivo* (mice) indicated that the phenols did cross the BBB and traces of the compounds were detected in the brain and GBM tissue [37]. The fenofibric acid phenols are believed to inhibit GBM proliferation *via* reducing metabolic activity (ATP production), resulting in apoptosis of GBM with cell death. This is very similar to the experiments that were performed with curcumin [32].

Thus, the development of prodrug glycosylated fenofibric phenols that inhibit GBM cellular replication appear to be a promising viable approach to penetrating the BBB and cytotoxic therapy *vs* GBM.

5. Conclusion

An attempt to review the chemistry, neuropharmacology and preliminary results—*in vitro* and *in vivo*—has been made. DM-CHOC-PEN has been studied in depth, as therapy for both metastatic and primary malignancies involving the CNS. The latter is a bi-functional alkylating agent as discussed in this paper. However, minimal information is available regarding cytotoxic mechanisms of action for the polyphenolic structures described herein. The positive responses observed and reported are support for continued studies with the poly phenols as well as initiation of a Phase III clinical trial with DM-CHOC-PEN in GBM.

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Abbreviations

SRS	Stereo radiosurgery.
TMZ	Temozolamide.
DM-CHOC-PEN	4-demethyl-4-cholesteryloxycarbonylpenclomedine.

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