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New Approach for Enhancing Survival in Glioblastoma Patients: A Longitudinal Pilot Study on Integrative Oncology

Massimo Bonucci [1,*], MariaPia Fuggetta [2], Lorenzo Anelli [1], Carla Fiorentini [1], Diana Giannarelli [3], Giampietro Ravagnan [2]

[1] Association for Research on Integrative Oncology Therapies (ARTOI) Foundation, 00165 Rome, Italy
[2] Institute of Translational Pharmacology, National Research Council of Italy (CNR), 00133 Rome, Italy
[3] Facility of epidemiology & biostatistics, Policlinic University Foundation "A. Gemelli" IRCCS Rome, Italy
* Correspondence: maxbonucci@artoi.it

Simple Summary: GBM has a very poor prognosis, even in the short term, because it is one of the most aggressive malignancies and responds very poorly to any medical treatments. This work stems from the need to find ways to improve the therapeutic response to glioblastoma. In the group of 72 patients with glioblastoma, those who used natural substances such as polydatin, curcumin and boswellia serrata in combination with the STUPP radio-chemotherapy treatment (60 patients) showed improved survival (from 13.3 months to 25 months of median survival). This study, if further supported by in-depth studies, opens the way for new therapeutic combinations.

Abstract: This study evaluates the clinical outcomes of 72 patients with glioblastoma multiforme (GBM), focusing on integrative treatment (IT). The overall survival (OS) for all patients was 13.3 months, while those who received IT demonstrated significantly improved outcomes. Among the 65 patients who underwent IT, OS increased to 16.3 months. In the subgroup with high adherence (60 patients), OS extended to 25.4 months. The one-year survival rate for highly adherent patients was 59.0%, compared to 53.1% in the larger study population. In addition to survival benefits, IT contributed significantly to improved treatment tolerance. Patients receiving IT experienced fewer side effects from radiotherapy, including reduced post-radiation edema and fatigue. Blood counts remained stable, thereby permitting uninterrupted chemotherapy cycles. These findings underscore IT as a valuable addition to standard therapies, enhancing both survival and quality of life. Updated data further reinforce IT's impact: the median survival for highly adherent patients now exceeds 55 months, with a survival rate of over 25%, far surpassing the international five-year survival rate of 3-7%. At the study's conclusion, ten patients remained alive, highlighting IT's potential to improve long-term outcomes in GBM treatment.

Keywords: glioblastoma; Stupp protocol; metilation; integrative oncology; herbal medicine; polidatyn; curcumin; boswellia serrata

Introduction

Glioblastoma multiforme (GBM), classified as a WHO grade IV astrocytoma, is the most common and aggressive type of brain tumor in adults. It has a poor prognosis, with recurrence rates of 100% [1]. GBM comprises approximately 50% to 60% of adult astrocytomas and about 12% to 15% of intracranial neoplasms. The median age at diagnosis is 64 years, with an estimated incidence of 2 to 3 cases per 100,000 individuals in Europe and North America (4). GBM can arise as a 'primary' or 'de novo' tumor or may develop from the progressive transformation of more differentiated forms, known as 'secondary'. The secondary form of GBM primarily affects younger patients, with a frequency of 5%. In contrast, the primary form predominantly impacts older patients, with a frequency of 95% [3]. The 2021 WHO classification for central nervous system (CNS) tumors

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mandates the presence of mutations in isocitrate dehydrogenase 1 and 2 (IDH-wildtype) and histone 3 (H3-wildtype) for a diagnosis of GBM [2]. This classification introduces molecular criteria for diagnosing histologically lower-grade, IDH-wildtype astrocytomas as glioblastoma, IDH-wildtype (WHO grade IV) [5]. These newly proposed classifications aim to specify the prognosis associated with the diagnosis, as the absence of these mutations leads to a significantly poorer prognosis compared to their presence. Neoplasia is not directly caused by specific genetic damage; instead, gene mutations often enhance its aggressiveness. Commonly affected genes include those that inhibit oncosuppressor genes, such as p53, HIC-1, p16, 22q-19q LOH, and PTEN, as well as those that activate oncogenes like CDK4, MDM2, EGFR, or the IDH 1-2-3 mutation. These mutations play a critical role in the neoplastic transformation of glial cells, which is essential for distinguishing primary glioblastomas from secondary ones [6]. Certain glioblastomas exhibit multiple sub-clonal amplifications of distinct receptor tyrosine kinase genes, such as MET, EGFR, and PDGFRA, within the same tumor [7]. Additionally, telomerase reverse transcriptase (TERT) promoter mutations have been identified as the most common oncogenic mutation in glioblastoma, affecting up to 80% of cases [8]. TERT is the protein component of telomerase, responsible for maintaining telomere length in cells with high replicative potential [9]. Telomerase activation addresses this issue and grants cells the ability to divide indefinitely, achieving cellular immortality. *TERT* promoter mutations occur in approximately 80% of IDH- wildtype glioblastomas [8,10] and in up to 28% of IDH- mutant glioblastomas [10]. These mutations in gliomas are known to be prognostically significant, as their presence is associated with poor outcomes [11]. Evaluating MGMT methylation status is critically important because the absence of methylation leads to increased drug resistance [12]. Patients with tumors harboring an inactivated MGMT gene due to promoter methylation (present in approximately 35-45% of patients) are significantly more likely to respond to Temozolomide compared to those whose MGMT gene remains functional. MGMT methylation acts as a favorable prognostic factor, although within the context of an unfavorable disease trajectory [13]. The genetic aberrations in individuals with glioblastoma vary considerably, often even within the same tumor. Consequently, any specific “effective” treatment agent will only benefit a minority of patients, as it targets only one or occasionally two growth pathways, allowing other pathways to be upregulated and sustain tumor growth. A pathophysiological hallmark of glioblastoma is the expression of VEGF and other pro- angiogenic cytokines, which promote endothelial cell proliferation, migration, and survival [14]. This leads to the formation of highly abnormal tumor vasculature, marked by hyperpermeable vessels, increased vessel diameter, and abnormally thickened basement membranes. Widespread tumor infiltration is one of its distinguishing features, making it rarely circumscribed. Other notable features of this neoplasm include abnormal neovascularization, cellular pleomorphism, and high mitotic activity alongside necrosis, all contributing to the term ‘multiform’[15]. Furthermore, glioblastoma stem cells, resistant to drug therapies, can migrate from the tumor and disseminate to various brain regions [16,17]. Identifying all tumor extensions into normal tissue is additionally challenging, as cancer cells are often located far from the primary tumor, suggesting possible metastases within the brain. Nevertheless, most tumor recurrences occur within or near the original tumor site. Even if localized treatment eradicates 99% of the tumor, a small residual fraction will expand geometrically, leading to clinical complications. As a result, surgical therapy alone can only prolong survival without providing a cure for those afflicted by this disease [18,19]. GBM tumorigenesis is characterized by high production of lipids derived from arachidonic acid, which stimulates the development of peritumoral cerebral edema and tumor progression [20].

Surgical resection [21], along with associated radiotherapy and subsequent administration of adjuvant temozolomide (TMZ), a derivative of the alkylating agent dacarbazine, is the gold standard treatment for glioblastoma multiforme (GBM) with a grade of 3 or higher [22].TMZ provides a significant advantage in terms of progression-free survival (PFS), with a median of 6.9 months compared to 5 months, and overall survival (OS), with a median of 14.6 months compared to 12.1 months [23].

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The superior efficacy of chemotherapy combined with radiotherapy, compared to radiotherapy alone, has been demonstrated. [24]. Monoclonal antibody bevacizumab, along with alkylating agents such as carmustine, lomustine, nimustine, and fotemustine, is also employed in the treatment of GBM [25–28]. Regrettably, despite diligent efforts, most novel therapeutic approaches proposed, including targeted-based therapy, exhibit limited efficacy in clinical trials [29]. A study conducted by the University of Padua revealed that the use of an anti-angiogenic drug, Regorafenib, in treating relapsed glioblastoma multiforme (GBM) significantly increased survival duration by approximately seven months. Given the dismal prognosis associated with GBM, characterized by a median overall survival of 14.6 months, these multimodal therapies have often proven ineffective. Furthermore, these treatments are not without adverse effects, which can be severe [30]. Radiotherapy, in particular, necessitates a consistent dosage of steroids to mitigate or treat cerebral edema and elevated intracranial pressure [31]. Glucocorticoids are the most effective medications currently available for treating cerebral edema, although they are associated with a wide range of adverse effects [32]. The current limitations of treatment necessitate the development of novel drugs that exhibit enhanced efficacy, reduced side effects, and more favorable prognoses.

Natural products demonstrate various potentials, including enhanced bioavailability and increased stability when interacting with active constituents [25]. Patients use traditional herbal medicine to bolster their immune systems, leading to the inhibition of tumor development and progression, which facilitates the survival of cancer patients [26]. Consequently, complementary treatments, those that do not interfere with conventional therapies while enhancing disease management, minimizing side effects, and improving patients' quality of life (QoL), should be integrated to glioblastoma multiforme (GBM) treatment [33]. Additionally, preclinical in vitro studies have shown that certain natural compounds can inhibit duplication and proliferation, induce apoptosis, or restore telomerase activity in malignant glioblastoma cells [34]. Certain herbal medicines have shown efficacy in treating glioblastoma multiforme (GBM) based on their ability to modulate angiogenesis, metastasis, endoplasmic reticulum (ER) stress, reactive oxygen species (ROS), multidrug resistance (MDR), and microRNA expression. This is achieved through increased stability, protection from toxicity, enhanced pharmacological activity, improved tissue macrophage distribution, and defense against physical and chemical degradation. Extracts from plants such as *Angelica sinensis* [35], inositol hexaphosphate [36], *Nigella sativa* seed oil [37], *Scutellaria baicalensis* (Lee 2012), *Caesalpina sappan* [38], *Artemisia argyi* [39], and *Tithonia diversifolia* [40] exhibit apoptotic action in glioblastoma cells. Other extracts from *Garcinia mangostana* [41] and *Balanites aegyptiaca* [42] have been shown to generate reactive oxygen species (ROS) in glioblastoma. Extracts from *Panax ginseng* (Rg3) [43], *Cannabis sativa* [44], *Vitis vinifera* [45], and Magnolol [46] exhibit an antiangiogenic effect on glioblastoma cells. *Camellia sinensis* [47], *Tinospora cordifolia* [48], Resveratrol [49], and Curcumin [11] have demonstrated antimetastatic properties in glioblastoma cells. Natural polyphenols are a diverse and extensively distributed class of bioactive compounds characterized by their structural composition of one or more aromatic rings bearing one or more hydroxyl groups [50]. Numerous studies have shown the beneficial effects of polyphenols as antioxidants, anti-inflammatories, antitumors, and antivirals [51]. Previous research has established that polyphenols possess antioxidant properties, acting as free radical scavengers. These compounds effectively reduce oxidative stress, which is believed to contribute to the pathogenesis and progression of various chronic and acute diseases [52]. In clinical research, oxidative stress has been linked to a variety of degenerative diseases, including cancer and inflammatory conditions [53]. In recent years, numerous epidemiological studies have examined the role of polyphenols in the etiology and progression of cancer [54]. Many scientific studies have confirmed that curcumin (CUR), the primary constituent of the Indian culinary spice turmeric (Curcuma longa), exhibits anti-cancer properties across a wide range of tumor types, including GBM [55]. Curcumin, known for its anti-inflammatory and antioxidant properties, modulates a diverse spectrum of cellular signaling pathways, leading to the inhibition of cell proliferation and induction of apoptosis [56]. Polydatin (PD), another polyphenolic compound, functions as a phytoalexin, a naturally occurring substance found in various plant

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species, including Polygonum cuspidatum [57]. Polydatin is a glycosylated form of Resveratrol (RSV) and the most abundant derivative of resveratrol in nature [58]. Numerous studies have investigated the beneficial effects of PD/RSV on the human body, including their antioxidant, anti-inflammatory, antitumor, antiviral, neuroprotective, hepatoprotective, and ischemia-preventing activities. Additionally, the mechanisms of action of PD/RSV have been elucidated [59–61]. In particular, PD has the potential to inhibit proliferation, migration, invasion, and stemness in GBM cells while simultaneously inducing apoptosis [62]. Both PD and CUR are widely used alone or in combination in the pharmaceutical and nutraceutical fields as drugs or food supplements. Although combinations of RSV and/or PD +CUR are proposed for tumor treatment, no studies currently examine the use of CUR and PD in combination with conventional treatments in GBM [63]. Curcumin and polydatin have exhibited the ability to modulate the expression of various growth factors, including VEGF, FGF, PDGF, HIF-1, TNF-alpha, MMP-9, and Cox-2. These substances exhibit potent anti-inflammatory activity by reducing the levels of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, IL-12, and IL-17. They also influence the expression of Bax and Bcl-2 and suppress p53, leading to anti-oedematous and pro-apoptotic effects. Furthermore, they appear to inhibit neoplastic cell growth by blocking cyclin D1 and c-myc.

The primary objective of this pilot study is to investigate the efficacy of curcumin (CUR) and polydatin (PD) alongside conventional therapies for a small cohort of patients with glioblastoma multiforme. The study primarily aims to ascertain improvements in quality of life and increases in survival rates among GBM patients treated with these therapies. Additionally, Boswellia serrata (BS) extract has been included in the treatment regimen to alleviate the edema associated with GBM and minimize reliance on glucocorticoids [64]. According to Yadav et al., this plant has been used for centuries in traditional Ayurvedic medicine to address a wide range of inflammatory conditions [65]. The antitumor properties of Boswellia serrata are linked to the downregulation of various biomarkers associated with inflammation, cell proliferation, cell survival, invasion, and angiogenesis [66]. Boswellia serrata has been extensively researched for its anti-oedemigenic properties [67]. It exerts anti-inflammatory effects by acting on NF-kB, Cox-2, and LO-5 [68]. To date, however, only limited data are available on the effects of BS on brain edema and brain tumors [69].

Although the mechanisms of action for many natural products are well-known, it remains unclear whether using multiple remedies simultaneously can lead to better outcomes [70]. This study, for the first time, examined whether combining various natural substances could provide a clinical therapeutic advantage in glioblastoma treatment.

Materials and Methods

Patients

Patients with newly diagnosed, histologically confirmed de novo glioblastoma multiforme (WHO grade IV) who underwent surgery (or biopsy), radiotherapy, and chemotherapy with temozolomide (TMZ) were enrolled in this longitudinal pilot study after providing their written informed consent. The study adhered to the Helsinki Declaration and received approval from the institutional ethics committee. A total of 72 patients with GBM were included, having been followed and treated from September 2012 to March 2017 at the Oncology Unit of a Roman hospital. The primary inclusion criteria were:

- Age of 18 years or older
- Histological evidence of glioblastoma
- Clinical and radiographic evidence of brain cancer
- All patients diagnosed radiologically with a probable neoplastic lesion of cerebral origin underwent surgical biopsy for histological diagnosis.
- Patients, when possible, underwent surgery for neoplasm removal.

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- In all cases, biological parameters and the assessment of the lesion's methylation status (MGMT) were studied.

Radiochemotherapy and Complementary Treatment

All patients underwent 30 sessions of whole-brain radiotherapy (radiation treatment). The radiotherapy provided 59.4 Gy in 30 daily fractions (1.8-2 Gy for each fraction), totaling 6 weeks of treatment. It commenced within 28 to 30 days following surgery, coinciding with the expected healing process. In conjunction, temozolomide (TMZ) chemotherapy was administered daily, starting with the radiotherapy and continuing until its completion. When feasible, TMZ was continued for an additional month after the treatment's conclusion, following a 4-week chemotherapy-free interval. Patients received up to six cycles of maintenance (adjuvant phase) TMZ (150-200 mg/sqm for 5 days during each 28-day cycle). This regimen was given daily for 5 days every 28 days. Patients continued therapy with steroids at the initial prescribed dose; any modifications were evaluated during clinical visits, considering the edema assessed on MRI and the patients' medical condition.

Integrative treatment (IT) was achieved using a pharmaceutical formulation known as Composition (Table 2). This formulation combines Polydatin PD (CAS number 27208-80-6) and Curcumins CUR. Curcumins CUR consists of Curcumin I, Curcumin II, and Curcumin III. The Composition used for IT contained approximately 2 mg to 4 mg of PD and 2 mg to 5 mg of CUR per kilogram of body weight, depending on the patient's physical condition. The pharmaceutical formulation of Composition (gel and/or mouth-soluble tablet) was administered daily for at least six weeks during the radiotherapy treatment cycle and preferably for the remainder of the patient's life. In the formulation, the active compounds are mixed with a carrier that possesses the necessary binding properties in suitable proportions.

Table 2. Integrative Treatment Details for Patients with Glioblastoma Multiform.

Component	Composition	Dosage	Administration Schedule
Main Composition			
Polydatin (PD)	CAS number 27208-80-6	2-4 mg per kg of body weight	Daily
Curcumins (CUR)	Mixture of Curcumin I, II, and III	2-5 mg per kg of body weight	Daily
Administration Forms			
Acute phase (up to 1 year)	PD + CUR	500 mg of Composition daily	For at least 6 weeks during radiotherapy and continuing through acute phase
Maintenance phase	PD + CUR	300 mg of Composition daily	For the rest of patient's life
Pharmaceutical Formulation			

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Delivery method	Gel and/or mouth-soluble tablet	-	-
Adjunct Treatment			
Boswellia serrata extract	Phytosome-based delivery form of boswellic acids	1.8-2.4 g total dose per day	Daily
Supportive Treatments			
For hematological parameters alterations	Goat colostrum	-	As needed during Temozolomide treatment
	Tamarix gallica extracts	-	As needed during Temozolomide treatment
	Melatonin	-	As needed during Temozolomide treatment
	Glutathione	-	As needed during Temozolomide treatment

Two administration intervals were identified: one related to the acute phase and another pertaining to the maintenance phase. During the acute phase, which can last up to one year, patients receive at least 500 mg of the Composition daily. In the maintenance phase, which can extend for the remainder of the patient's life, patients received 300 mg of the Composition daily. Patients commenced treatment with the Composition from the start of their diagnosis. Some patients, however, opted to initiate IT during various phases of conventional treatment. Of the 72 patients who participated in the study, 7 (9.7%) had never received therapy, and an additional 5 (6.9%) were not compliant with the IT protocol, meaning they did not consistently adhere to medical prescriptions.

The composition has been administered alongside a compound of *Boswellia serrata* extract that possesses anti-edema activity. This innovative phytosome-based delivery form of boswellic acids is provided at a dosage range of 1.8 to 2.4 grams per day. During treatment with Temozolomide, patients underwent thorough monitoring of all five vital parameters (hematological and urinary tests) as well as instrumental examinations (CT and MRI) to evaluate disease progression. If hematological parameters (white blood cells, red blood cells, platelets, liver enzymes) were altered during Temozolomide treatment, certain natural substances, such as goat colostrum, Tamarix gallica extracts, melatonin, and glutathione, were administered to mitigate the effects. Instrumental examinations were repeated every three months following the completion of radiotherapy for a minimum of two years, subsequently shifting to every six months throughout the study period. Patients adhered to a specialized nutrition regimen recommended by ARTOI Foundation (Table 3). The diet excludes red and white meat, milk and dairy products, simple and complex sugars, and foods containing polyamines, while the intake of fruits and soy is reduced.

Table 3. Dietary Regimen for Patients with Glioblastoma Multiforme.

Dietary Category	Recommendation	Details/Rationale
Foods to Exclude		

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Meat	Completely excluded	Both red and white meat
Dairy	Completely excluded	Milk and all dairy products
Sugars	Completely excluded	Both simple and complex sugars
Polyamine-rich foods	Completely excluded	Foods containing high levels of polyamines [71]
Soy products	Completely excluded	Limited consumption recommended
Foods to Reduce		
Fruit	Reduce intake	Limited consumption recommended
Dietary Framework		
Dietary structure	Specialized nutrition regimen recommended by ARTOI	According to ARTOI guidelines
Implementation timing	Begin at diagnosis and continue throughout treatment	Concurrent with conventional and integrative treatments
Dietary Rationale		
Cancer metabolism	Reduce glucose availability	GBM cells are highly dependent on glucose metabolism
Inflammation	Reduce inflammatory dietary components	Support anti-inflammatory effects of integrative treatments
Polyamine pathway	Reduce dietary polyamines	May influence tumor growth [71]
Monitoring		
Adherence assessment	During follow-up visits	Part of overall treatment adherence evaluation
Nutritional status	Regular assessment	To prevent malnutrition

Statistical Analysis

Overall survival was measured from the date of definitive glioblastoma diagnosis or the initiation of IT, as appropriate, to the date of death or the most recent follow-up available. Survival curves were estimated using the Kaplan-Meier method and compared via the log-rank test. Median survival time and corresponding 95% confidence intervals were reported. Baseline comparisons were analyzed using the $\chi 2$ test. A P-value of less than 0.05 was deemed statistically significant. All statistical analyses were performed using SPSS version 21.0.

Results

As shown in Table 1, the patient population consisted of 42 males (58%) and 30 females (42%). The average age was 57 years (range: 18-85 years). Among these patients, 66 (91.7%) had undergone surgery, with complete resection achieved in 28 cases (42.4%). A total of 69 patients (95.8%) had received radiotherapy. Six patients (8.3%) had not undergone any chemotherapy, while 53 (73.6%) had received chemotherapy. Of these, 52 patients were treated with TMZ, and only one received Nimotuzumab plus Vinorelbine. Eleven patients (15.3%) had a second treatment, primarily

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consisting of fotemustine. Two patients (2.8%) underwent a third treatment, which included one BCNU Carmustine combined with a PCV conjugated pneumococcal vaccine and one rituximab.

Table 1. Caption.

Characteristic	Value	Percentage
Total number of patients	72	100%
Gender distribution		
- Male	42	59%
- Female	30	41%
Age		
- Median	57 years	
- Range	18-85 years	
Surgical intervention		
- Patients who underwent surgery	66	91.7%
- Complete resection	28	42.4% of surgical patients
- Biopsy/partial resection only	38	57.6% of surgical patients
- No surgical intervention	6	8.3%
Radiotherapy		
- Patients who underwent radiotherapy	69	95.8%
Chemotherapy		
- Patients who underwent only first line chemotherapy	53	73.6%
- Second-line treatment	11	15.3%
- Third-line treatment	2	2.8%
- No chemotherapy	6	8.3%
Corticosteroid treatment		
- At the beginning of the study	31	43.1%
Average time from diagnosis to first visit	3.9 months	
- Range	10 days - 14 months	
Adherence to integrative treatment		
- Never received integrative therapy	7	9.7%
- Non-adherent to protocol	5	6.9%
- High adherence to protocol	60	83.3%

Patients with GBM visited our center for the first time, on average, 3.9 months after diagnosis, with a range of 10 days to 14 months. At the time of their initial visit, 31 patients (43.1%) had received corticosteroids.

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The overall survival (OS) of all 72 treated patients was 13.3 months (95% confidence interval CI: 7.3-19.3). Concerning the treatment type, Table 4 shows that among the 72 patients, surgical intervention was prevalent, with 91.7% undergoing some form of surgery. Complete resection was

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achieved in 42.4% of cases, while 57.6% underwent either a partial resection or biopsy. Radiotherapy played a crucial role, with 95.8% of patients receiving this treatment.

Table 4. Treatments Received by Patients with Glioblastoma Multiforme.

Treatment Type	Number of Patients	Percentage
Surgical Intervention		
- Complete resection	28	38.9%
- Partial resection/Biopsy only	38	52.8%
- No surgery	6	8.3%
Radiotherapy		
- Received radiotherapy	69	95.8%
- Did not receive radiotherapy	3	4.2%
Chemotherapy - First Line		
- Temozolomide (TMZ)	52	72.2%
- Nimotuzumab + Vinorelbine	1	1.4%
- No first-line chemotherapy	19	26.4%
Chemotherapy - Second Line		
- Fotemustine (primarily)	11	15.3%
- No second-line chemotherapy	61	84.7%
Chemotherapy - Third Line		
- BCNU Carmustine + PCV conjugated pneumococcal vaccine	1	1.4%
- Rituximab	1	1.4%
- No third-line chemotherapy	70	97.2%
Integrative Treatment (IT)		
- Received and highly adherent to IT	60	83.3%
- Received but not adherent to IT	5	6.9%
- Never received IT	7	9.7%
Corticosteroid Treatment		
- Received at beginning of study	31	43.1%
- Did not receive at beginning of study	41	56.9%

Fifty-three patients underwent chemotherapy. In first-line chemotherapy, temozolomide (TMZ) was the most common choice, at 72.2%, while 26.4% did not receive any chemotherapy. Alternative regimens, such as Nimotuzumab combined with vinorelbine, were rarely utilized, accounting for only 1.4%. Second-line chemotherapy was less prevalent, with just 15.3% receiving fotemustine, whereas the majority, at 84.7%, did not receive treatment. Third-line chemotherapy was even less common, with only two patients receiving additional treatment, resulting in 97.2% without further chemotherapy. Regarding integrative treatment (IT), a large proportion (83.3%) were highly adherent; 6.9% received IT but were not adherent, and 9.7% never participated in it. Lastly, corticosteroid use was divided: 43.1% received it at the start of the study, while 56.9% did not.

The treatment approach for this patient group was highly standardized, primarily utilizing radiotherapy and temozolomide (TMZ) as the main therapeutic strategies. Although most patients underwent surgery, complete resection was achieved in only about a third of cases. The use of second- and third-line chemotherapy was less frequent, indicating that treatment intensity decreased

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as the disease progressed. Furthermore, integrative treatments were widely embraced, reflecting a trend toward supportive care. The variability in corticosteroid use indicates differences in strategies for managing symptoms. This data illustrates a typical treatment pathway for patients, emphasizing the importance of multimodal therapy while showing that aggressive interventions become less common in later stages.

As shown in Table 5, the median overall survival (OS) for the 65 patients who received integrative treatment was 16.3 months (95% confidence interval [CI]: 0.2-32.4). The series of 60 patients who demonstrated high adherence to the therapy achieved a median OS of 25.4 months (95% CI: 8.3-42.5). The one-year survival rate for the entire series was 53.1%, with a 55.4% rate for the 65 patients treated. The series of 60 patients who exhibited high adherence achieved a one-year survival rate of 59.0%.

Table 5. Overall Survival Results for Patients with Glioblastoma Multiforme Who Received Integrative Treatment.

Patient Group	Number of Patients	Median Overall Survival (months)	95% Confidence Interval	1-Year Survival Rate	2-Year Survival Rate	5-Year Survival Rate
All patients	72	13.3	7.3-19.3	53.1%	-	16.0%
Patients who received integrative treatment	65	16.3	0.2-32.4	55.4%	-	-
Patients with high adherence to integrative treatment	60	25.4	8.3-42.5	59.0%	-	25.0%
Patients who underwent complete surgery with high adherence	28	34.4	18.1-40.8	82.4%	54.2%	34.0%

Additional Survival Data

- **Survivors at study conclusion**: 10 patients remained alive at the end of the study
- **Long-term survivors**: Approximately 12% of total patients (increasing to >16% in the IT protocol group) survived beyond 60 months
- **Median survival update**: For the sample of survivors, median survival now exceeds 55 months

Comparison with Literature

Source	5-Year Survival Rate
Current study (all patients)	16.0%
Current study (complete surgery + high adherence)	34.0%
Literature references	3-7%

No significant differences in survival were observed based on gender, age, or the number of previous chemotherapy treatments (Table 6). Notably, the one-year survival rates were 51.9% for males and 59.1% for females. For younger patients (<57 years), the one-year survival rates were 53.8%, while older patients had rates of 57.0%. Patients who received only one chemotherapy treatment had

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a one-year survival rate of 58.0%, compared to 56.3% for those who underwent two or three treatments. Additionally, patients who received corticosteroids had a one-year survival rate of 58.7%, whereas those who did not received a rate of 50.6%. The overall average survival across the entire series varied depending on the extent of surgical intervention. Patients who did not undergo surgery had a one-year survival rate of 18.3%, those who had complete surgery achieved a one-year survival rate of 74.0%, and patients who only had a biopsy had a one-year survival rate of 56.4%. The median overall survival for this group from the time of diagnosis was 34.4 months (95% CI: 18.1-40.8), with a one-year survival rate of 82.4% and a two-year survival rate of 54.2%.

Table 6. Survival Results by Patient Subgroups in Glioblastoma Multiforme.

Characteristic	Subgroup	Number of Patients	One-Year Survival Rate	Statistical Significance
Gender				No significant difference
	Male	42	51.9%	
	Female	30	59.1%	
Age				No significant difference
	<57 years	35	53.8%	
	≥57 years	37	57.0%	
Number of Previous Chemotherapy Treatments				No significant difference
	One treatment	53	58.0%	
	Two or three treatments	13	56.3%	
Corticosteroid Use				No significant difference
	Received corticosteroids	31	58.7%	
	Did not receive corticosteroids	41	50.6%	
Extent of Surgical Intervention				P<0.001
	No surgery	6	18.3%	
	Complete resection	28	74.0%	
	Biopsy/Partial resection	38	56.4%	

When the side effects were considered (Table 7), unexpected results were noted with IT, including a reduction in the adverse effects of radiotherapy. Specifically, there was a decrease in post-

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radiation edema and post-radiation fatigue, the latter of which has not yet been published. The platelet count among the 60 patients was normal, as were the white and red blood cell counts. These findings allowed for chemotherapy treatment to continue without interruption for all desired cycles.

Table 7. Side Effects and Management for Patients with Glioblastoma Multiforme.

Side Effect Category	Conventional Treatment Side Effects	Observations with Integrative Treatment	Management Strategy
Radiotherapy Effects			
Post-radiation edema	Common and severe, typically requiring increased steroid use	Decreased in the integrative treatment group	Boswellia serrata extract (1.8-2.4 g/day) used to mitigate edema and reduce reliance on glucocorticoids
Post-radiation fatigue	Common complaint affecting quality of life	Decreased in the integrative treatment group	Integrative treatment protocol (PD + CUR)
Hematological Parameters			
Platelet count	Often decreased during chemotherapy, potentially leading to treatment interruption	Normal in the group of 60 highly adherent patients	Regular monitoring and supportive treatments when needed
White blood cell count	Often decreased during chemotherapy	Normal in the group of 60 highly adherent patients	Goat colostrum, Tamarix gallica extracts as supportive treatments
Red blood cell count	Often decreased during chemotherapy	Normal in the group of 60 highly adherent patients	Supportive treatments when needed
Liver Function			
Liver enzymes	Often elevated during chemotherapy	Not specifically reported	Supportive treatments including glutathione when needed
Chemotherapy Continuation			
Treatment interruption	Common due to side effects	All desired cycles completed without interruption in the integrative treatment group	Regular monitoring and prompt management of side effects
Glucocorticoid Dependence			

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Steroid use for cerebral edema	Common, with associated adverse effects	Reduced need for steroids	Boswellia serrata extract for its anti-oedemigenic properties

Discussion

Glioblastoma, a highly aggressive neoplastic disease, has a dismal five-year prognosis as of my last update [1]. Diagnosis typically occurs when the lesion is extensive, and significant surgery often proves unfeasible due to unfavorable prognostic factors [1]. This condition can arise from the evolution of low-grade glial lesions that, over time, acquire aggressive characteristics through specific mutations, resulting in increased malignancy [6]. GBM carries a poor prognosis, with patients rarely achieving prolonged survival. Even with multimodal therapies such as radiotherapy, chemotherapy, and surgery, the prognosis remains challenging. Notably, surgery has been correlated with more favorable outcomes. Currently, concomitant chemotherapy with alkylating agents, particularly Temozolomide, is the standard approach for treating glioblastoma. The median survival is approximately 18 months, while the five-year survival rate ranges from 2% to 7% [23]. The various treatments available today, including biological and immunotherapeutic approaches, as well as those involving nanoparticles or radiometabolic strategies, do not seem to alter the survival rates of these patients significantly. However, they often demonstrate a substantial burden of adverse effects that severely restrict their comprehensive application [29]. Given the aggressive nature of glioblastoma, which frequently exhibits resistance to radio- and chemotherapy, along with the adverse effects associated with these modalities, there is an urgent need for a novel and appropriate alternative or adjuvant treatment for glioblastoma.

Over the past few decades, there has been a growing interest in using herbal and natural compounds, or their derivatives, which tend to be less toxic, for various therapeutic purposes, particularly in cancer treatment. Natural substances have consistently demonstrated efficacy in promoting antineoplastic activity against high-grade glial cells in both in vitro and in vivo studies. Furthermore, in the management of glioblastoma, over 50% of patients utilize complementary and alternative approaches, with herbal therapies being the most commonly employed empirically [33]. Glucosidic stilbenoids, such as resveratrol and curcumin, are widely utilized in the pharmaceutical industry, either alone or in combination. US Patent 2009/0047371 describes the application of resveratrol and curcumin compositions for treating prostate tumors and inflammatory diseases, including psoriasis and other skin conditions. However, there is currently no evidence suggesting that the combination of PO and CUR can effectively treat tumors in the Central Nervous System (CNS). The synergistic effects of curcumin alongside radiotherapy and chemotherapy illustrate its potential in treating glioblastoma multiforme (GBM). Curcumin stands out as an exemplary natural pharmaceutical compound capable of crossing the blood-brain barrier (BBB). Additionally, its lipophilic nature promotes favorable absorption, availability, and retention within the CNS [72]. Numerous scientific studies have explored the various pharmacological effects of curcumin, which include antimicrobial, anti-inflammatory, antioxidant, and notably, anticancer properties [55]. In this context, curcumin has been recognized as an effective anti-tumor agent against GBM [11]. The anticancer properties of curcumin encompass modulation of cell proliferation, induction of apoptosis, inhibition of angiogenesis, induction of autophagy, stimulation of the immune response, and inhibition of cell invasion and metastasis [56]. Despite its potential therapeutic benefits, the use of curcumin is limited due to its low intestinal absorption and pharmacokinetics [73,74]. After repeated administration of curcumin in humans, the blood serum concentration peaked at approximately 2 μM [75], which may be insufficient for effective anticancer action. Curcumin exhibits a remarkably low toxicity profile, and numerous clinical studies have demonstrated its well-tolerated and safe nature (Clinicaltrials.gov 2019). Polydatin is a polyphenolic compound that acts as a phytoalexin, a naturally occurring substance found in various plant species, including Polygonum cuspidatum [57]. Polydatin is the glycosylated form of resveratrol (RSV) and represents the most abundant derivative

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of resveratrol in nature [58]. Many studies have investigated the beneficial effects of PD/RSV on the human body, highlighting their antioxidant, anti-inflammatory, antitumor, antiviral, neuroprotective, hepatoprotective, and ischemia-preventing activities. Furthermore, the mechanisms of action of PD/RSV have been elucidated [59–61]. Specifically, PD can inhibit proliferation, migration, invasion, and stemness in GBM cells while inducing apoptosis. A variety of conventional chemotherapeutic agents are used to treat GBM, including temozolomide, doxorubicin, paclitaxel, and others. Several studies have shown that resveratrol can enhance the therapeutic efficacy of these chemotherapeutic agents through various mechanisms, which will be discussed in detail below [59]. Resveratrol has been demonstrated to significantly improve the radiosensitivity of cancerous cells in both in vitro and nude mouse models. This effect is attributed to its synergistic anticancer properties, including inhibition of self-renewal and stemness, induction of apoptosis, induction of autophagy, and inhibition of DNA repair [76]. Self-renewal is a fundamental characteristic of stem cells, and this capacity of cancer stem cells (CSCs) is crucial for tumorigenesis and tumor progression [77]. CSCs possess stemness potential, indicating that proliferative cancer cells are continuously renewed through the asymmetric division of CSCs [78]. A study involving glioblastoma multiforme (GBM) patients who were referred to an oncology outpatient clinic and received standard care (the STUPP protocol), followed by second- and third-line anticancer drugs, was conducted. As part of the adjunctive protocol, herbs such as polydatin, curcumin, Boswellia serrata, and nutritional recommendations from the American Society of Clinical Oncology (ASCO) were implemented.

The study included all patients who visited the oncology outpatient clinic at S. Feliciano Hospital in Rome between 2012 and 2017. The study cohort comprised 72 patients. Among them, seven patients did not receive IT therapy, 5 either did not adhere to the IT protocol or did so for less than 4 months, while the remaining 60 patients consistently followed the protocol. All patients provided consent for participation and additional treatment. The results obtained from these patients were significant, revealing a median survival of 25 months, with 10 patients surviving beyond 60 months (approximately 12% of the total number of patients, which increases to over 16% in the IT protocol group). Finally, when compared with literature data on glioblastoma, the results of this study clearly show the benefits of utilizing integrative treatment (Table 8). The sample of survivors is highly significant, with a median survival time now exceeding 55 months. The current survival rate is over 25% among those closely adhering to the protocol (60 out of 72 patients). In contrast, the total study population exhibits a survival rate of 16%. The subgroup that underwent complete surgery had an overall survival rate of 34%, while the international 5-year survival rate ranges from 3 to 7% [1,3,6,12,13,15,18,20,23]. At the conclusion of the study, ten patients remained alive.

Table 8. Comparing Study Results with Literature Data on Glioblastoma Multiforme.

Outcome Measure	Current Study Results	Literature Data	Difference	Reference Citations
Median Overall Survival				
All patients (n=72)	13.3 months	12.1-14.6 months	Comparable	[23]
Patients who received integrative treatment (n=65)	16.3 months	12.1-14.6 months	+1.7 to +4.2 months	[23]
Patients with high adherence to integrative treatment (n=60)	25.4 months	12.1-14.6 months	+10.8 to +13.3 months	[23]

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Patients who underwent complete surgery with high adherence	34.4 months	~18-19 months*	+15.4 to +16.4 months	[19,23]
1-Year Survival Rate				
All patients (n=72)	53.1%	~50%	+3.1%	[1,3]
Patients who received integrative treatment (n=65)	55.4%	~50%	+5.4%	[1,3]
Patients with high adherence to integrative treatment (n=60)	59.0%	~50%	+9.0%	[1,3]
Patients who underwent complete surgery with high adherence	82.4%	~61-65%*	+17.4 to +21.4%	[1,3,19]
2-Year Survival Rate				
Patients who underwent complete surgery with high adherence	54.2%	~25-30%*	+24.2 to +29.2%	[1,3,6]
5-Year Survival Rate				
All patients (n=72)	16.0%	3-7%	+9.0 to +13.0%	[1,3,6,12,13,15,18,20,23]
Patients with high adherence to integrative treatment (n=60)	25.0%	3-7%	+18.0 to +22.0%	[1,3,6,12,13,15,18,20,23]
Patients who underwent complete surgery with high adherence	34.0%	3-7%	+27.0 to +31.0%	[1,3,6,12,13,15,18,20,23]
Long-term Survival (>60 months)				
All patients (n=72)	12%	<3%	>+9.0%	[1,3,6]
Patients with high adherence to integrative treatment (n=60)	16%	<3%	>+13.0%	[1,3,6]

- **Survivors at study conclusion**: 10 patients remained alive at the end of the study
- **Long-term survivors**: Approximately 12% of total patients (increasing to >16% in the IT protocol group) survived beyond 60 months
- **Median survival update**: For the sample of survivors, median survival now exceeds 55 months

Comparison with Literature

Source	5-Year Survival Rate
Current study (all patients)	16.0%
Current study (complete surgery + high adherence)	34.0%
Literature references	3-7%

This observational study aimed to clarify the potential synergistic effects of natural substances when paired with conventional chemotherapy and radiotherapy methods. The study showed that these patients maintained hematological standards that allowed them to receive a broader range of anticancer treatments. The use of a multimodal treatment regimen, which includes the aforementioned innovation, acts as a valuable adjunct in extending the survival of patients with brain tumors. Furthermore, this approach ensures a satisfactory quality of life for these individuals. The data presented here reveals a significant improvement in the survival rate of patients undergoing treatment for glioblastoma, as evidenced by their continued existence and better symptomatology.

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Limitations of the Study

Several limitations of the study must be acknowledged. This was a preliminary investigation that lacked a double-blind, randomized design. Although 72 cases were evaluated, seven patients did not receive integrated therapy and can be considered a control group. Therefore, the study lacks proper control group and randomization. The research focused on first-onset glial neoplasms. To ensure consistent validation of the treatment with Curcumin, Polydatin, and Boswellia, the study should be expanded to include patients with glioblastoma relapses, allowing for the evaluation of the effects on reducing or blocking proliferative activity. Preliminary unpublished studies indicate a synergistic effect with Temozolomide, which may lead to the development of a relapse prevention strategy using low-dose Temozolomide in conjunction with Curcumin and Polydatin. Extensive resection may contribute to some of the observed benefits.

Previous studies involving patients with varying degrees of resection suggest that complete tumor removal may extend survival by approximately 4 to 5 months compared to partial resection [19]. However, when considering the total number of survivors, only 16% truly experienced the benefits at the 5-year follow-up. This figure varies significantly in literature, ranging from two to five times. This discrepancy deserves careful consideration and should encourage us to collaborate on innovative approaches to improve cure rates and ultimately ensure salvation for everyone.

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