Complementary and Alternative Medicine for the Treatment of Gliomas: Scoping Review of Clinical Studies, Patient Outcomes, and Toxicity Profiles

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■ INTRODUCTION: **Complementary and alternative medicine (CAM) are highly used among those diagnosed with glioma. Further research is warranted, however, as it remains important to clearly delineate CAM practices that are unproven, disproven, or promising for future research and implementation.**

■ METHODS: **A systematic review was conducted to identify all articles that investigated the effect of any CAM therapy on survival of patients with newly diagnosed or recurrent glioma.**

■ RESULTS: **Eighteen papers and 4 abstracts pertaining to the effects of ketogenic diet (4), antioxidants (3), hyperbaric oxygen (4), cannabinoids (2), carbogen and nicotinamide (3), mistletoe extract (2), hypocupremia and penicillamine (1), and overall CAM use (3) on overall and progression-free survival in patients with low- and high-grade glioma were identified (Levels of Evidence I-IV). Ketogenic diets, hyperbaric oxygen therapy, and cannabinoids appear to be safe and well tolerated by patients; preliminary studies demonstrate tumor response and increased progression-free survival and overall survival when combined with standard of care therapies. Antioxidant usage exhibit mixed results perhaps associated with glioma grade with greater effect on low-grade gliomas; vitamin D intake was associated with prolonged survival. Conversely, carbogen breathing and hypocupremia were found to have no effect on the survival of patients with glioma, with associated significant toxicity. Most modalities under the CAM umbrella have not been appropriately studied and require further investigation.**

■ CONCLUSIONS: **Despite widespread use, Level I or II evidence for CAM for the treatment of glioma is lacking, representing future research directions to optimally counsel and treat glioma patients.**

INTRODUCTION

Upwards of 30% of patients with glioma use complementary and alternative medicine (CAM) therapies in addition to standard of care (SOC) therapy.[1] However, no comprehensive reviews exist exploring the current status of CAM therapies for glioma treatment. CAM therapies are defined as any practices outside standard medical care, including herbal supplements, dietary modifications, acupuncture, meditation and mindfulness, yoga, and traditional Chinese and Ayurvedic therapies, among others.[2]

Given the current cultural context in which CAM usage is widespread and increasing, a general understanding of CAM

Key words
- Alternative medicine
- Complementary medicine
- Glioblastoma
- Glioma

Abbreviations and Acronyms
CAM: Complementary and alternative medicine
CBD: Cannabinoid
CI: Confidence interval
GBM: Glioblastoma
HBO: Hyperbaric oxygen
HGG: High-grade glioma
HR: Hazard ratio
KD: Ketogenic diet
LGG: Low-grade glioma
ML-1: Mistletoe lectin 1
OS: Overall survival
PFS: Progression-free survival
SOC: Standard of care
TAI: Total antioxidant intake
TMZ: Temozolamide
TTP: Time to progression

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therapies is imperative for appropriate patient counseling and determination of future research directions. Here, we systematically review the current clinical evidence assessing various CAM therapies in patients diagnosed with primary gliomas. Our review builds on the existing literature by incorporating all forms of CAM therapy, all subtypes of glioma, and focusing on clinical outcomes and toxicity profiles versus use patterns. Accordingly, we provide a comprehensive description of the clinical landscape of CAM therapies in an effort to direct patient guidance, clinical decision-making, and future research directions.

METHODS

Definition of CAM

A systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for Scoping Reviews to identify all studies relating to the usage of CAM therapies for glioma treatment (Supplementary Figure 1).[3,4] PubMed and EMBASE databases were searched from January 1990 to August 2019 using the following Medical Subject Headings terms: complementary therapy (including alternative therapy), acupuncture, yoga, therapeutic touch, reiki, electroacupuncture, mindfulness, meditation, herbal medicine, Chinese Medicine, Ayurveda, diet, traditional medicine, ascorbic acid, cannabis, glioma, glioblastoma, malignant glioma. CAM modalities were derived from previous methodologies and Medical Subject Headings (MeSH) subheadings to ensure completeness of the search.[5,6]

Article inclusion criteria were as follows:

- involved adult patients with newly diagnosed or recurrent high-grade glioma (HGG) or low-grade glioma (LGG);
- included progression-free survival (PFS) and/or overall survival (OS) time as a primary outcome of measure; and
- case series, retrospective, or prospective studies.

Article exclusion criteria were as follows:

- non-English publications;
- basic science papers;
- case reports;
- animal studies;
- review articles;
- studies on pediatric gliomas only;
- risk analyses;
- papers investigating the effectiveness of accepted medical management of glioma (chemotherapy, immunotherapy, surgery, radiation, etc.);
- Papers investigating anesthesia outcomes; and
- Papers that did not clearly separate glioma outcomes from those of other cancers.

Conference presentations and abstracts that met inclusion criteria were included. The inclusion of this "gray literature" is multifold, as it reduces publication bias and allows for broader exploration of CAM glioma treatment.

Literature Search Results

The initial search yielded a total of 2369 records, and 1547 remained after duplicates were removed (Supplementary Figure 1). Two independent reviewers (H.C.B., E.K.) screened abstracts for relevance and after subsequent full-text analysis 22 studies met full inclusion/exclusion criteria to be included in the final analysis following arbitration by the entire research team.

Nineteen studies analyzed the effect of specific classes of CAM (antioxidants, ketogenic diet, cannabinoids, hyperbaric oxygen, carbogen breathing/nicotinamide, hypocupremia, hyperbaric oxygen, and mistletoe) on survival, and 3 cohort studies analyzed the use of any CAM and its effect on survival.

RESULTS

This review identified 18 papers and 4 abstracts pertaining to the effects of ketogenic diet (4), antioxidant therapy (3), carbogen and nicotinamide therapy (3), mistletoe extract (mistletoe lectin 1 [ML-1]) (2), hyperbaric oxygen (HBO) therapy (4), cannabinoids (CBD) (2), hypocupremia and penicillamine (1), and overall CAM use (3) on overall and PFS in patients with LGG and HGG. These studies consisted of Levels of Evidence I–IV with 1 randomized, placebo-controlled study, 7 nonrandomized controlled clinical trials, 10 clinical trials without control, 2 single-institution retrospective database reviews, and 4 patient questionnaire studies. Proposed mechanisms of actions are described within each section and additionally summarized in Supplementary Table 1.

Ketogenic Diet (KD)

The KD is a low-carbohydrate, high-fat diet that aims to shift the body's primary energy source from glucose to ketones with the goal of limiting glycolysis, the main energy source of tumor cells, thereby limiting tumor proliferation.[7] Four studies examined the effect of KD in gliomas, consisting of 3 Level II and 1 Level III studies.[8-11] Santos et al.[8] studied KD as adjuvant therapy with intranasal perillyl alcohol in 17 patients with recurrent glioblastoma (GBM; 9 KD, 8 control) and saw tumor reduction in 7 of 9 patients on the KD (78%) versus 2 of 8 control (25%). Progression occurred in 1 of 9 patients on the KD (11%) versus 4 of 8 controls (50%). Tumor size was smaller ($P = 0.035$) in the KD group compared with baseline and not in the control group ($P = 0.687$). However, the study design precludes an understanding of effectiveness related to KD versus perillyl alcohol.

Dardis et al.,[9] in a cohort study of KD used in conjunction with radiation and temozolomide (TMZ) in 14 patients, found median time to progression (TTP) was 7 months and OS was 29.3 months in patients on a KD. Champ et al.[10] found that patients on a KD had a median TTP of 10.3 months, and 4 of 6 patients were alive at 14 months. The ERGO trial prospectively examined the effect of KD on 20 patients with recurrent GBM. Median PFS on the diet was 5 weeks; patients who maintained ketosis showed an insignificant trend toward longer PFS than those who did not ($P = 0.069$)[11] (Table 1). These studies suggest a

Table 1. Studies Investigating the Effect of the Ketogenic Diet on Progression and Survival Time in Patients with Gliomas

Study, year	Study Design (*n*)	Relevant Outcomes
Santos et al., 2018[8]	Controlled clinical trial ($n = 32$)	Decreases of ≥30% in tumor size were noted in 78% of patients with recurrent GBM treated with 3 months of ketogenic diet with intranasal perillyl alcohol compared with 25% in the standard diet group. Progression was seen in 1 of 9 (11%) in the treatment group versus 4 of 8 (50%) in the standard diet group.
Dardis et al., 2017[9]	Single-institution clinical trial ($n = 14$)	On an intention-to-treat basis, median time-to-progression was 7 months and overall survival was 29 months in 14 patients with GBM on the ketogenic diet
Champ et al., 2014[10]	Retrospective single-institution database review ($n = 6$)	Four of 6 patients (67%) with GBM on the ketogenic diet were alive at median follow-up of 14 months
Rieger et al., 2014[11]	Single-institution clinical trial ($n = 20$)	Median progression-free survival in 20 patients with recurrent GBM on ketogenic diet was 5 weeks, and patients who maintained stable ketosis had a nonsignificant trend toward longer progression-free survival

GBM, glioblastoma.

potential benefit for KD as an adjunctive therapy, although randomized clinical trials should be performed to fully understand its effectiveness.

Antioxidant Therapy

The effects of antioxidants are unclear. Antioxidants may protect normal brain parenchyma commonly damaged during SOC (radiation and/or chemotherapy), thereby leading to improved outcomes. Others believe antioxidants may actually protect tumor cells from free radical–mediated DNA damage and induction of apoptosis by radiation and chemotherapy.[12] Three studies examined the use of antioxidant therapy in gliomas, consisting of 1 Level II study and 2 Level III studies[13-15] (Table 2). In a case–control study including patients with HGG, no association was seen between total antioxidant index (TAI) (calculated from food frequency questionnaires 1 year prediagnosis) and OS.[13] When patients' standard therapy included TMZ, a weakly significant association was observed between TAI and increased OS (Model 1: hazard ratio [HR] 0.88, confidence interval [CI] 0.82–0.94; Model 2: HR 0.58, CI 0.46–0.74); however, it became insignificant when controlling TMZ.[13] For LGG, moderate to high intake of folate, vitamin E, secoisolariciresinol, and formononetin were associated with prolonged OS.[14] Conversely, DeLorenze et al.[14] observed a negative association between OS time and the highest tertile of self-reported TAI in patients with grade IV gliomas. Secoisolariciresinol, formononetin, cryptoxanthin, matairesinol, vitamin C,

Table 2. Studies Investigating the Effects of Antioxidants and/or Dietary Changes on Progression and Survival Time Patients with Gliomas

Study (year)	Study Design (n)	Relevant Outcomes
Il'yasova et al., 2009[13]	Patient questionnaire ($n = 814$)	No significant association was noted between overall survival and antioxidant intake or combination with vitamin supplements in patients with GBM receiving standard of care therapy
DeLorenze et al., 2010[14]	Patient questionnaire ($n = 784$)	Grade II gliomas: Moderate intake of water-soluble folate and moderate total protein intake were associated with greater overall survival whereas high intake of vitamin C, genistein, and the greatest antioxidant levels were all associated with poorer overall survival. Moderate intake of fat-soluble lycopene was associated with worse overall survival compared with low intake. Grade III gliomas: High intake of vitamin E, moderate/high intake of secoisolariciresinol, moderate intake of formononetin were associated with greater overall survival. Moderate intake of fat-soluble lycopene and alpha-carotene was associated with worse overall survival compared to low intake. Grade IV gliomas: High total protein intake was associated with improved overall survival. Moderate/high intake of cryptoxanthin, high intake of secoisolariciresinol, moderate intake of formononetin, high intake of vitamin C and genistein, moderate cholesterol intake, and high antioxidant intake were associated with poorer overall survival.
Puri et al., 2010[15]	Placebo-controlled clinical trial ($n = 50$)	Lycopene was associated with an insignificantly longer time to progression in patients with high-grade gliomas who underwent surgical resection followed by radiotherapy and chemotherapy

GBM, glioblastoma.

Table 3. Studies Investigating the Effect of Adjuvant HBO Therapy on Overall Survival and TTP in Patients with Malignant Glioma

Study	Study Design (n)	Relevant Outcomes
Beppu et al., 2003[22]	Single-institution clinical trial ($n = 39$)	35 of 39 patients (90%) tolerated HBO therapy. Median TTP was 46 weeks (38 weeks for glioblastoma, 56 weeks for anaplastic astrocytoma)
Koshi et al., 1996[19]	Single-institution Controlled clinical trial ($n = 21$)	9 of 9 patients (100%) with malignant gliomas treated with HBO therapy adjuvant to radiotherapy saw partial or complete tumor regression, compared with 4 of 12 patients (33%) in the control group. 4 of 9 patients (44%) treated with HBO showed complete response and 3 of 4 (75%) had no recurrence after more than 40 months. The fourth patient demonstrated recurrence at 40 months after therapy. All 12 patients undergoing conventional chemoradiotherapy without HBO showed recurrence or progression and died within 36 months after therapy.
Koshi et al., 1999[20]	Multi-institution Controlled clinical trial ($n = 29$)	11 of 15 patients (73%) with malignant gliomas receiving HBO therapy adjuvant to radiotherapy showed partial or complete response, with 9/11 (82%) showing immediate response and 2 of 11 (18%) showing delayed response 6 months after therapy completion. 4/14 patients (29%) in the non-HBO group showed partial regression at completion of therapy, with 1 of 4 (25%) showing complete response 4 months after therapy ended. All 14 patients developed tumor growth or recurrence and died within 36 months of diagnosis (median survival 12 months). 4 of 9 patients (44%) receiving HBO experienced recurrence, with median survival of 24 months. HBO adjuvant therapy significantly increased survival rate.
Ogawa et al., 2012[21]	Single-institution clinical trial ($n = 57$ total, 11 underwent GTR)	7 of 46 patients (15%) with high-grade gliomas receiving HBO therapy adjuvant to chemoradiotherapy showed complete response, 17 of 46 (37%) showed partial response, 21 of 46 (46%) had stable disease, and 1 of 46 (2%) showed disease progression. Median TTP was 71.1 months for grade 3 gliomas and 9.6 months for GBMs. 2-year progression free survival was 71% in grade 3 gliomas and 16% in GBMs. 8 of 57 patients (14%) experienced middle-ear barotrauma requiring tympanostomy with tube placement and 6 of 57 (11%) experienced nausea treated with pre-HBO treatment metoclopramide.

HBO, hyperbaric oxygen; TTP, time to progression; GTR, gross total resection; GBM, glioblastoma.

genistein, and cholesterol were associated with poorer survival in patients with GBM and HGG.[14]

Lycopene is a carotenoid and potent antioxidant that has shown promise in treating heart disease[16,17] and may have antiproliferative and anticarcinogenic[15] properties useful for glioma treatment. In a placebo-controlled clinical trial with patients with HGG, the addition of lycopene as adjuvant therapy to SOC therapy was associated with significantly greater median follow-up time (66.29 weeks vs. 38.71 weeks; $P = 0.05$).[15] Although not an appropriate proxy for survival, greater median follow-up time may indicate either longer survival or longer maintenance of quality-of-life measures. Patients in the lycopene-supplemented group also experienced a nonsignificant improved TTP ($P = 0.089$).[15] In patients with LGG, however, moderate dietary lycopene intake in the year before diagnosis was associated with poorer survival compared with low dietary intake (Grade II: HR 2.31, CI 1.12–4.75; Grade III: HR 2.17, CI 1.02–4.62).[14] The opposing outcomes reported in patients treated with antioxidants harboring LGG versus HGG may represent important differences in tumor metabolism and physiology (Table 2).

Hyperbaric Oxygen (HBO)

Hypoxia is theorized to play a role in the resistance of malignant glioma to radiotherapy. During radiation, oxygen serves as a crucial and potent radiosensitizer in the chemical reaction that damages DNA in cancer cells.[18] Accordingly, the use of HBO to increase oxygenation in glioma tissue has been proposed as an adjuvant therapy to radiotherapy. Two Level II studies and two Level III studies investigated the utility of HBO in treatment of malignant glioma[19-22] (Table 3). HBO was generally well tolerated. Kohshi et al.[19] compared HBO with radiotherapy ($n = 9$) to radiotherapy alone ($n = 12$) and found 100% partial or complete tumor regression with no recurrence at 40 months in 75% of the HBO group, compared with 33% tumor response and 100% recurrence with subsequent mortality by 36 months in the control group. A subsequent study by the same group found partial or complete responses to HBO with radiotherapy in 74% of patients versus in 29% of patients without HBO; they also found HBO to significantly increase OS (24 vs. 12 months). One study found average TTP was 46 weeks for those treated with HBO with no control group.[22] A more recent trial of 57 patients found 15% of patients with HGG receiving HBO showed complete response to radiotherapy with a median TTP of 71.1 months for grade 3 glioma and 9.6 months for GBM. Fourteen percent of patients experienced middle ear barotrauma.[21]

Carbogen and Nicotinamide as Adjuncts to Radiotherapy

Inhaled carbogen (95% O^2) and coadministration of intravenous nicotinamide is thought to reverse tumoral hypoxia and increase sensitivity to radiotherapy.[23-26] Three studies examined the use of

Table 4. Studies Investigating the Effect of Carbogen Breathing on Progression and Survival Time in Patients with Gliomas

Study (year)	Study Design (*n*)	Relevant Outcomes
van der Maazen et al., 1995[26]	Single-institution clinical trial ($n = 16$)	Median survival in patients with high-grade gliomas treated with carbogen was 223 days postresection (patients were concomitantly treated with radiotherapy and carbogen breathing). Four of 16 patients (25%) had elevated liver enzymes, 2 of 16 (13%) experienced severe nausea/vomiting, and 2 of 16 (13%) experienced neurologic and psychiatric disturbances.
Miralbell et al. 1999[28]	Single-institution clinical trial ($n = 107$)	Median survival in patients with GBM undergoing radiotherapy treated with carbogen ($n = 23$) was 10.1 months (PFS 6.7 months), in patients treated with nicotinamide ($n = 28$) was 9.7 months (PFS 4.8 months), and in patients treated with carbogen + nicotinamide was 11.1 months (PFS 5.8 months). No significant difference in survival or PFS was noted when compared with historic patients treated with radiotherapy alone. Patients experienced significant skin and gastrointestinal toxicity side effects.
Simon et al., 2003[27]	Controlled clinical trial ($n = 33$)	Nicotinamide and carbogen used with radiotherapy in patients with inoperable GBM did not significantly improve median survival time compared with radiotherapy alone (36.7 vs. 35.3 weeks). Nicotinamide was associated with severe side effects.

GBM, glioblastoma; PFS, progression-free survival.

carbogen and nicotinamide in gliomas, consisting of 3 Level II studies[26-28] (Table 4). Sixteen patients with malignant gliomas undergoing conventional radiotherapy in conjunction with carbogen breathing and nicotinamide had a median survival of 233 days, which not superior compared with historical data. Treatment was associated with elevated liver enzymes (4/16 patients, 25%), severe nausea and vomiting (2/16 patients, 13%), and visual hallucinations and paranoia (2/16 patients, 12.5%).[26] A phase I/II trial of carbogen and nicotinamide as adjuncts to accelerated radiotherapy supported these findings, with adverse effects of skin toxicity (53%), mucous membrane toxicity (4%), gastrointestinal toxicity (44% nicotinamide, 32% combined carbogen and nicotinamide), and epilepsy. Median OS for patients treated with carbogen adjunct, nicotinamide adjunct, and combined carbogen and nicotinamide adjunct was estimated at 10.1 months (PFS 6.7 months), 9.7 months (PFS 4.8 months), and 11.1 months (PFS 5.8 months), respectively. No treatment group showed significantly improved OS compared with historical survival with radiotherapy alone.[28] Simon et al.[27] compared nicotinamide and carbogen as adjuncts over a longer period (6.5 weeks) and further supported that nicotinamide associated nausea, vomiting, and toxicity. In addition, nicotinamide and carbogen did not improve median OS compared with radiotherapy alone (36.7 and 35.3 weeks respectively, $P = 0.79$) (Table 3). Together, these findings suggest severe toxicities and marginal effect on OS or PFS.

Cannabinoids (CBD)

Multiple plant-derived cannabinoids, including cannabidiol and delta-9-tetrahydrocannabinoil, have shown promise as adjuvant therapies in animal models for treating GBM, which express cannabinoid-specific receptors.[29] Two studies (one Level I study published as an abstract, and one Level III study) investigated CBD as an adjuvant therapy.[30,31] A case series of 9 patients receiving CBD as adjuvant therapy alongside SOC demonstrated a mean OS of 22 months and no deaths at time of publication.[30] One Level I, double-blind study compared oro-mucosal CBD:delta-9-tetrahydrocannabinoil sprays ($n = 12$) with a placebo ($n = 9$) in

Table 5. Studies Investigating the Effect of a Mistletoe-Extracted Galactoside-Specific Lectin (ML-1) on Overall Survival and Quality of Life in Patients with Gliomas

Study (year)	Study Design (n)	Relevant Outcomes
Lenartz et al., 2000[37]	Placebo-controlled clinical trial ($n = 38$)	Patients with high-grade gliomas treated with adjuvant galactoside-specific lectin extracted from mistletoe (ML-1) alongside standard of care demonstrated improved overall survival compared with the control group and an insignificant trend towards longer relapse-free survival.
Lenartz et al., 1996[38]	Placebo-controlled clinical trial ($n = 35$)	Patients with high-grade gliomas treated with ML-1 adjuvant therapy demonstrated increased CD-3, CD-4, and CD-8 cell counts as well as activities of CD-25 and HLA/DR after 3 months and improved patient quality of life.

ML-1, Mistletoe lectin 1.

conjunction with SOC. One-year survival was 83% in the CBD group, versus 56% in the control group ($P = 0.042$), although OS was not significantly different between the groups.[31]

Other Adjunctive Therapies

Hypocupremia. Dietary copper is a required cofactor for angiogenesis and stimulates endothelial cell proliferation.[32,33] HGGs (GBM) show the greatest degree of angiogenesis of all tumors[34]; therefore, antiangiogenic therapies including dietary copper restriction (hypocupremia) and copper-chelating agents (D-penicillamine) are potentially therapeutic.[32,35] One Level II study (phase II clinical trial) involved 40 patients with newly diagnosed glioblastoma maintaining a low copper diet (0.5 mg/day) and administering penicillamine, a copper chelator (250–2000 mg/day). Although hypocupremia was achieved and tolerated, there was no significant difference in mean OS between experimental and control groups (6 months: 77.5%/80.5%, 12 months: 45%/50.8%, 18 months: 30%/24.6%, respectively).[32]

Mistletoe. ML-1 is a galactoside-specific lectin extracted from mistletoe that has been shown to improve quality of life and immunologic rescue in patients with cancer.[36] Two Level II studies examined the use of ML-1 in gliomas[37,38] (Table 5). A prospective randomized clinical trial of 38 patients with HGG receiving either SOC or SOC complemented with ML-1 treatment (1 ng/kg) found no significant difference in relapse-free survival (17.43 ± 8.2 months vs. 10.45 ± 3.9 months). However, the ML-1 group showed improved OS when compared with the SOC group ($P = 0.035$, 20.05 ± 3.5 months vs. 9.90 ± 2.1 months, respectively).[37] In another study, the same authors demonstrated adjunctive therapy with ML-1 significantly increased CD-3, CD-4, and CD-8 cell counts as well as activities of CD-25 and HLA/DR after 3 months and improved patient quality of life ($n = 35$).[38] This promising result should encourage further research into plant extracts as adjunctive therapies (Table 5).

Use of Any Form of CAM. Literature regarding CAM usage overall is sparse, and the little that exists shows mixed findings. A self-reporting study of 470 patients with GBM found usage of nutritional or herbal supplements, including multivitamins or any other individual supplement while concurrently undergoing SOC treatments, was unrelated to OS. However, vitamin D intake (13% of patients) was associated with prolonged survival after adjusting for age ($P = 0.019$) and in multivariate analysis ($P = 0.043$).[39] Randazzo et al.[40] used the International CAM Questionnaire for 365 patients with GBM and found no association between the use of CAM and OS. Ambady et al.[41] conducted a retrospective review of 25 patients with GBM and found 36% of patients used some form of CAM, the most common being the homeopathic medications Ruta-6, curcumin, and hydroxychloroquine. They found no difference between CAM users and non-users in OS (17 months for CAM, 20.5 months for non-CAM). Taken together, these studies reveal little to no association between CAM use and prolonged survival.

DISCUSSION

Up to one third of patients with glioma have reported using CAM therapies,[42-44] and up to 74% did not disclose this information to their treating physician,[45] due to opposition or perceived opposition to CAM therapies by physicians.[46] Oncologists should be informed of adjuvant therapies to prevent drug interactions and monitor potential side effects. We have reviewed current data on a variety of available CAM therapies utilized to treat gliomas.

Potential Candidates for Exploration

The KD is a leading therapy for exploration, given its favorable effects in the studies analyzed and favorable tolerance profile. While multiple studies demonstrated an increase in PFS when KD was used alongside SOC therapy, the small sample sizes studied warrant larger trials with better randomization and controls. KD is a strong candidate due to its limited side effect profile and high degree of tolerability.[47,48] Its effectiveness should be re-reviewed in the near future, as multiple clinical trials with KD as adjuvant therapy are currently enrolling participants.[49-52]

Antioxidant therapy may warrant further exploration as the varied effects of specific antioxidants in low vs high-grade tumors have been demonstrated.[14,15] However, antioxidant therapy is a broad, "catch-all" term, and further investigation into specific antioxidants that may function as adjuvant therapies in GBM management is needed. Analyzing the category as a whole may mask potential therapeutic and/or harmful effects. While current level of evidence for antioxidant therapy is weak and largely based on self-reported retrospective patient questionnaires, the varying response profiles to antioxidants by LGG versus HGG may represent important differences in tumor metabolism, physiology, and/or adaptability. Due to the prevalence of antioxidants in media and marketing and its availability to patients, a thorough understanding of the mechanisms behind how specific antioxidant agents affect both tumor and chemoradiation therapy is prudent.

Similarly, exploration of vitamin D use as a CAM methodology may be warranted. One study found increased survival in patients who used vitamin D supplementation at doses greater than a regular multivitamin; however, usages were self-reported through structured interviews and further dosage implications or effect sizes could not be elucidated. The authors theorize that vitamin D may improve immune response to GBM or activate tumor suppressor gene p53; however, further exploration into mechanisms and prospective, controlled clinical trials are warranted.[39]

Clinical trials have demonstrated favorable toxicity profiles of HBO, and trials found improvements in survival in patients undergoing HBO-adjuvant radiation.[19,20] In addition, the use of HBO within current health care systems (e.g., treatment of decompression sickness, wound healing) would allow for integration as an adjunctive therapy.[53] Particularly in the context of improved radiotherapy techniques and precision in targeting lesions (where HBO is theorized to be most effective), HBO may portend improved survival for patients with malignant glioma.

The use of cannabinoids has seen widespread adoption among patients largely driven by increases in accessibility.[54] While its use is well established for symptomatic care of chemotherapy-associated pain and nausea, its possible antitumor effects are not as well described.[55] This review only noted 2 studies analyzing the effects of CBD, although further study is warranted given its widespread use.

Potential Risks of CAM Therapies

While many CAM therapies, such as yoga and meditation, have benign physiological effects,[56,57] pharmacologic agents (e.g.,

herbal supplements) used in conjunction with SOC or as an alternative pose additional risk. Unintended side effects, drug interactions, or even primary effects of CAM therapy can result in worse outcomes for patients with gliomas. Carbogen therapy with nicotinamide, for instance, was thought to aid in reversing the naturally hypoxic environment of glioma; however, patients experienced significant hepatotoxicity and gastrointestinal side effects with no concomitant increase in survival. CAM therapies may also interfere with or reduce the efficacy of chemotherapies.[58,59] Thorough analysis of polypharmacy is necessary when determining the effectiveness of CAM therapies as adjuncts, and there are no data to support this interaction among the CAM therapies discussed.

Challenges of CAM Therapy Investigation and Future Directions

A clear definition of CAM would improve patient–physician interaction and improve a clinician's ability to incorporate CAM into their assessment and treatment plans. In addition, few data exist for clinicians to use, particularly Level I evidence. The molecular mechanisms for many CAM therapies are poorly understood, and the research pipeline from in vitro to in vivo to clinical studies (especially randomized, controlled studies) needs to be more efficient. The National Institutes of Health currently funds less than $500,000 per year in funding for all CAM research, making the further investigation of these therapies fiscally challenging for scientists and clinicians, particularly for relatively rare diseases with poor prognosis like glioma.[60]

Limitations of Current Review

There are several limitations of the current review. Many of the studies have small sample sizes, which limit the ability to draw broad conclusions. In addition, the lack of prospective, randomized controlled studies creates the potential for confounding influences which include but are not limited to dosage, availability of SOC, use of multiple CAM therapies, and international differences in practicing/SOC. Patient questionnaire studies are additionally subject to response and sampling biases, among others.[61] Publication and selection bias are other limitations that may affect the validity of this systematic review.

CONCLUSIONS

The purpose of this scoping review was to highlight existing issues in current CAM literature and the discrepancy between the lack of evidence and the widespread usage of these modalities. Level I evidence (randomized, controlled prospective studies) for CAM as both standalone and adjuvant therapy is nonexistent, and Level II evidence is sparse and often lacks consensus. However, the widespread use of CAM among patients with glioma should prompt further exploration and understanding of potential risks and benefits via highly selective and appropriately designed studies.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Dhiraj J. Pangal: Conceptualization, Data curation, Methodology, Formal analysis, Validation, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Hans Baertsch:** Conceptualization, Data curation, Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Eliza M. Kellman:** Conceptualization, Data curation, Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Tyler Cardinal:** Data curation, Formal analysis, Validation, Visualization, Writing - original draft, Writing - review & editing. **Andrew Brunswick:** Validation, Writing - review & editing. **Martin Rutkowski:** Validation, Writing - review & editing. **Ben Strickland:** Validation, Writing - review & editing. **Frances Chow:** Validation, Writing - review & editing. **Frank Attenello:** Validation, Writing - review & editing. **Gabriel Zada:** Conceptualization, Data curation, Methodology, Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing.

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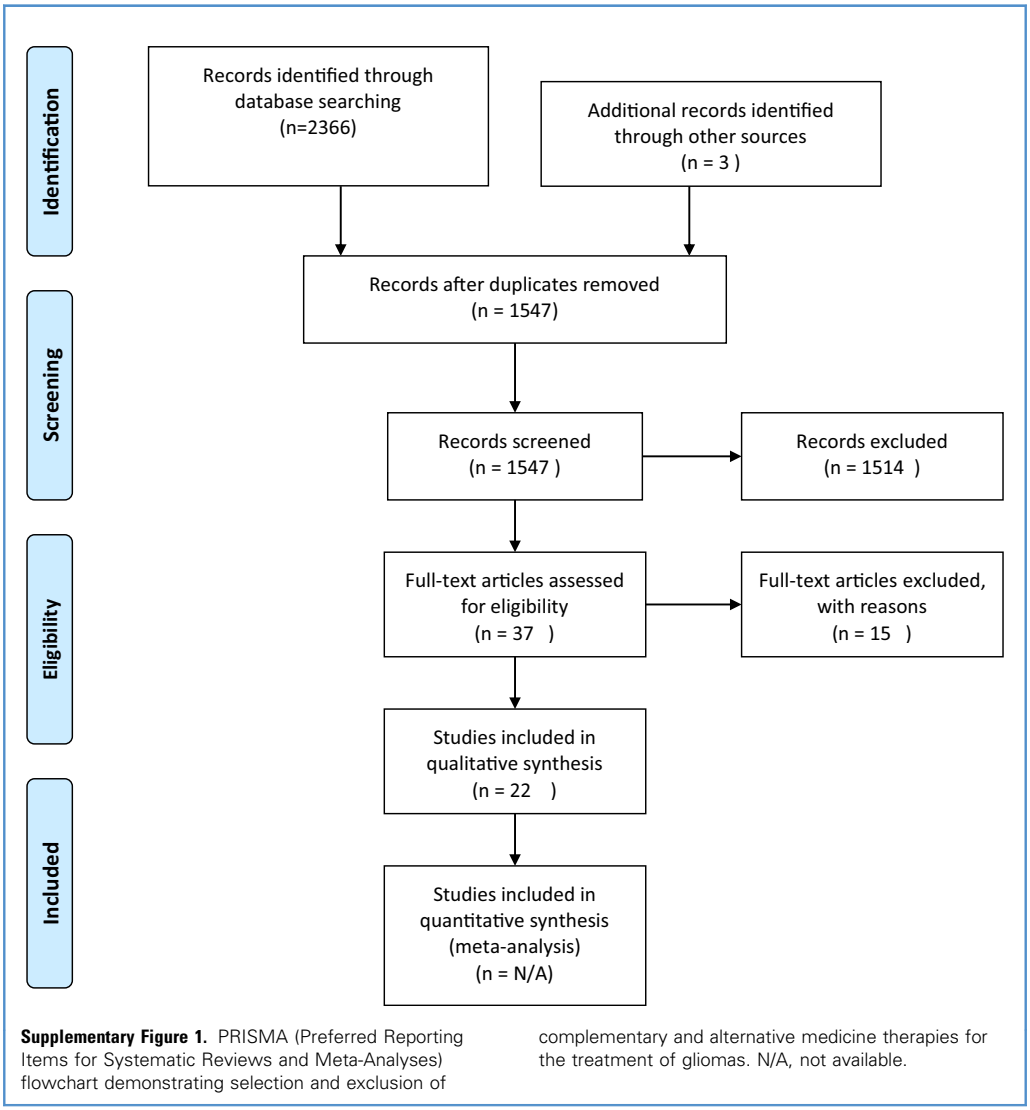
SUPPLEMENTARY DATA



Supplementary Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart demonstrating selection and exclusion of complementary and alternative medicine therapies for the treatment of gliomas. N/A, not available.

Supplementary Table 1. Hypothesized Mechanism of Action for Alternative Treatments for Glioma

Alternative Treatment	Key Component	Mechanism of Action
Ketogenic diet	β-hydroxybutyrate acetoacetate	Neoplastic cells depend on aerobic glycolysis for energy. Increased fatty acid oxidation elevates Acetyl-CoA levels to overwhelm the citric acid cycle, causing excess levels of ketone bodies (β-hydroxybutyrate and acetoacetate). Neoplastic cells cannot use these for metabolism as well as normal glial and neuronal cells can. Ketones also reduce ROS and inhibit angiogenesis, both shown to be important to cancer cell proliferation.
Antioxidant therapy	ROS	ROS may play important roles in tumorigenesis. Antioxidants can decrease ROS. However, this mechanism is not fully understood, and excess ROS has been shown to lead to cancer cell death, so reducing ROS may have drawbacks in glioma treatment.
Hyperbaric oxygen	HIF-1α	Insufficient oxygen increases angiogenesis and apoptosis, regulated by HIF-1. HIF-1α levels depend on cell oxygenation. Hyperbaric oxygen inhibits HIF-1α activity, theoretically improving tumor cell susceptibility to chemo and radiotherapy.
Carbogen + nicotinamide	HIF-1α ADP transferase	Carbogen decreases hypoxia, inhibiting HIF-1α activity and improving tumor cell susceptibility to radiotherapy. Unlike hyperbaric oxygen, carbogen includes carbon dioxide with the thought of increasing respiratory drive and causing vasodilation. However, it is less used now due to toxicity and side effects. Nicotinamide is theorized to inhibit repair of radiation-induced DNA damage via inhibition of adenosine diphosphoribosyl transferase (involved in DNA-excision repair). It also may prevent vascular shut-down and decrease perfusion-limited tumor hypoxia.
CB	Ceramide ROS	GBMs express cannabinoid receptors CB1 and CB2. Cannabinoids increase both ceramide and ROS production. Increased ceramides decrease angiogenesis, cell cycle activity and proliferation, and tumor invasion, while simultaneously increasing autophagy and apoptosis. ROS increase apoptosis and glioma stem cell autophagy, while also decreasing glioma stem cell renewal.
Hypocupremia	Copper cofactor	Copper is a required cofactor for angiogenesis and also stimulates endothelial cell proliferation. Decreased availability decreases angiogenesis and tumor blood flow required for growth and survival.
Mistletoe	Cytokine production	GBMs suppress the immune system via secretion of immunosuppressive cytokines and blocking T-cell activation while also increasing immunosuppressive regulatory T cells. ML-1 decreases tumor cell growth, induces apoptosis, and boosts anticancer immune responses. Specifically, it increases natural killer cell activity against glioma cells, causes monocyte-derived macrophage activity, dendritic cell maturation, and induced T-helper cell activation. Increased leukocytes and granulocytes as well as GM-CSF, IFN-γ, IL-5, IL-1β, IL-6, IL-10, and TNF-α have been seen in vivo in patients treated with ML-1.

ROS, reactive oxygen species; HIF-1, hypoxia-induced factor-1; ADM, adenosine diphosphate; GBM, glioblastoma; CB, cannabinoid receptor; ML-1, mistletoe lectin-1; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.