

Boswellia and Brain Tumors

By: Kirsten West, ND, LAc, FABNO



Boswellia shows potential in mitigating cerebral edema caused by radiochemotherapy.

Reference

Di Pierro F, Simonetti G, Petruzzi A, et al. A novel lecithin-based delivery form of Boswellic acids as complementary treatment of radiochemotherapy-induced cerebral edema in patients with glioblastoma multiforme: a longitudinal pilot experience. *J Neurosurg Sci.* 2019;63(3):286-291.

Objective

To assess the combination of phytosome-based boswellic-acids extract on radiochemotherapy-induced cerebral edema in patients undergoing treatment for glioblastoma multiforme (GBM)

Design

Pilot, longitudinal, nonrandomized, nonblinded clinical trial

Participants

Eighteen patients with a histologically verified, newly diagnosed GBM were included in this trial (7 women, 11 men). The median age of patients was 38 years (range 33-66 years). All patients underwent surgery (or biopsy), radiotherapy, and chemotherapy with temozolomide (TMZ). Inclusion criteria included a Karnofsky Performance Status of 70 or higher, concurrent treatment with dexamethasone (≤ 16 mg/day), and a Mental State Examination of 24 or greater.

Study Medication and Dosage

Patients received radiotherapy, TMZ, dexamethasone, and a phytosome-based formulation containing 32.2% boswellic acids (Casperome). Radiotherapy was given for a total of 6 weeks, which began within 28-30 days from surgery. TMZ was dosed at 75 mg/m² and was administered daily from the first to last day of radiotherapy. Patients resumed maintenance TMZ 4 weeks post radiation for up to 6 cycles at a dose of 15-200 mg/m² for 5 days during each 28-day cycle. Dexamethasone was given at baseline at a dose of ≤16 mg/day, and modifications were made per clinical assessment of cerebral edema as assessed by magnetic resonance imaging (MRI). Boswellia was dosed in the form of a phytosome-based delivery (Monoselect AKBA) at a dose of 4,500 mg/day (500 mg per capsule for a total of 9 capsules a day). Administration of Boswellia began with radiotherapy and continued to the end of maintenance TMZ for a maximum of 34 weeks.

Outcome Measures

Clinical evaluation, which included MRI, occurred at 4, 12, 22, and 34 weeks post-surgery and was denoted as T0, T1, T2, and T3 respectively.

The primary end point was the percentage of participants who either reached at least 75% decrease in their cerebral edema compared to baseline or had no edema at T1.

Peritumoral edema was classified according to a four-step scale: (1) significantly reduced edema (<25% compared to the previous MRI); (2) stable edema compared to the previous MRI; (3) slightly increased edema compared to the previous MRI; and (4) significantly increased edema (>50% compared to the previous MRI). All assessment was made per radiologist evaluation.

Secondary end points were:

- The percentage of those reaching >75% reduction in cerebral edema or showed no edema at all at T2 or T3.
- The percentage that achieved a reduction in their dexamethasone dose.
- Quality of life and psychological variables assessed at each time point.

Additionally, all patients were given standardized psychological assessments, at the intervals noted above, in the form of self-administered tests. These included: The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), EORTC QLQ Brain Cancer Module (EORTC QLQ-BN20), Beck Depression Inventory-II (BDI-II), Anxiety subscale of Hospital Anxiety and Depression Scale (HADS-A), Trait Anxiety subscale of State-Trait Anxiety Inventory Form Y (STAI-Y), and the Psychological Distress Inventory (PDI).

Key Findings

There were no statistical data regarding significance of assessed values in this study, nor any comparison with established data from other sources.

There were mixed results in this small cohort of patients with GBM undergoing radiation. Reduced edema (<25%) was constant during the study period in 4 patients (T1, T2, and T3). Reduced or stable edema tended to increase over time and was seen in 6 patients at 12 weeks (T1); 9 patients at 22 weeks (T2); and 7 patients at 34 weeks (T3). However, an increase of peritumoral edema was noted in 8 patients at 34 weeks (T3).

The dose of dexamethasone was either stable, reduced, or not utilized at all in the majority of patients. Six patients did not utilize any dexamethasone at 4 weeks (T0) and 12 weeks (T1) postsurgery, with 5 patients at 22 weeks (T2) and 4 patients at 34 weeks (T3) still able to remain off of dexamethasone. The percentages of patients who were able to take a stable or reduced dose of dexamethasone were 55.6%, 50%, 44.5%, and 37.6% at time points 4 weeks (T0), 12 weeks (T1), 22 weeks (T2), and 34 weeks (T3), respectively. While the trends appear to indicate some participants needed more dexamethasone due to increased cerebral edema, the authors note that the reduction of brain edema in 2 recurrent GBM patients may have offered a favorable surgical resection for those participants.

Overall, psychological assessments did not indicate a statistically significant change in any of the psychological scales over time. It appears that the majority of patients reported an acceptable or good quality of life. However, this value was missing in 4 patients. Mild anxiety was reported by the majority of patients throughout the study as recorded by the HADS-A scale.

Practice Implications

In 2019, there were approximately 17,000 new cases of high-grade gliomas diagnosed in the U.S. Glioblastoma multiforme (GBM) is a form of high-grade glioma and is the most aggressive malignant primary brain cancer. It accounts for about 60%-70% of all high-grade gliomas. Anaplastic astrocytomas, which can progress to GBM in some patients, account for the additional 30%-40%.^{1,2} These statistics make brain and other nervous-system cancers the 10th leading cause of death for men and women, with an incidence of about 3.19 per 100,000 persons and a median age at diagnosis of 64 years.³ GBM tends to afflict men more than women and is more common in Caucasians compared to Africans and African Americans, with the lowest incidence in Asians and American Indians.⁴ Although high-grade gliomas are relatively rare in children, other types of central nervous system (CNS) tumors together make up the second most common type of malignancy in children, following leukemia. Approximately 3,720 CNS tumors were diagnosed in 2019 in those under 15 years of age.^{5,6} Regardless of age, the 1-year survival for patients diagnosed with GBM is approximately 37.2%. This drops significantly to 5.1% at 5 years and 0.71% at 10 years.³ These statistics stand despite therapeutic advancements.

The causes of most brain cancers remain elusive. Risk factors may include previous radiotherapy, immune factors and immune genes, decreased susceptibility to allergy, and genetic susceptibility.⁷ There is some evidence that the use of anti-inflammatory medication may offer decreased susceptibility to the development of brain cancer.^{8,1} The use of cell phones has also been implicated as a cause of brain cancer. Although previous studies were inconclusive, recent data seem to justify precaution with high cellular-device use.^{9,10}

Several clinical trials have shown positive effects of *Boswellia* in inflammatory conditions.

To date, standard-of-care treatment involves optimal surgical resection followed by chemoradiation and maintenance TMZ for 6-12 months.^{11,12} Radiotherapy has been shown to significantly improve survival compared to surgery alone (3-4 months for surgery alone vs 7-12 months for surgery plus radiotherapy).^{13,14} In 2005, the U.S. Food and Drug Administration (FDA) approved TMZ for use as this, too, offered statistically significant improvement in progression-free survival (6.9 months with TMZ vs 5 months without TMZ) and overall survival (14.6 months vs 12.1 months).¹⁵ Despite these advancements, side effects from these therapies are unfavorable and often provide a major challenge in the management of brain cancer.

Cerebral edema and subsequent increased intracranial pressure are significant side effects that occur as a result of chemoradiotherapy.¹⁶ Glucocorticoids remain the primary method to manage edema; however, these are not without adverse effects. These adverse effects include: Cushing's syndrome, osteopenia, diabetes, immunosuppression, myopathy, gastrointestinal complications, irritability, anxiety, and insomnia, among others.¹⁷ Furthermore, these drugs may interfere with treatment efficacy, as they have been shown to influence vascular response to radiation, hinder apoptosis, and possibly increase activity of human glioma stem-like cells.¹⁸⁻²¹ Additional studies have shown that steroids may interfere with antitumor immune response secondary to standard therapies. A dose of more than 4.1 mg/day of dexamethasone decreased mean overall survival (OS) to 4.8 months versus 11 months mean OS in those who received less than 4.1 mg/day.²² Therefore, decreasing glucocorticoid use in those with GBM may not only serve to enhance immune response and increase efficacy of standard therapies but also increase overall survival.

Despite the many risks to glucocorticoids in brain cancer, they remain an accepted therapy due to the consequences of untreated cerebral edema, which is often debilitating. Dexamethasone is the most commonly employed glucocorticoid. Its dosing is typically consistent throughout treatment and is almost always required during radiation.¹ Unfortunately, glucocorticoids remain an essential part of treatment for many patients with GBM.

Given the dire statistics associated with high-grade gliomas and the side effects associated with standard of care, complementary therapies that serve to augment standard therapies are key. These therapies must fit within current models of care and lessen side effects of treatments without compromising efficacy. Furthermore, when considering a complementary therapy for brain tumors, it must cross the blood-brain barrier. *Boswellia* appears to meet these criteria.²³

Boswellia serrata (also known in Hindi as *salai* and *salai guggul*) grows in India, North Africa, and the Middle East.²⁴ Cultures originating in these countries have considered *Boswellia* a medicinal plant for hundreds of years. The sap of *Boswellia* is frankincense, and it is commonly used as incense in cultural and religious ceremonies. The plant itself is a large branching tree that grows in dry mountainous regions. Incisions made in its trunk allow for extraction of the oleo gum resin. This is then stored in a bamboo basket, which allows for the separation of oil from resin.²⁷

The gum resin extracts of *Boswellia* contain 4 primary pentacyclic triterpenic acids: β -boswellic acid, acetyl- β -boswellic acid, 11-keto- β -boswellic acid (KBA), and acetyl-11-keto- β -boswellic acid (AKBA).²⁵ The latter 2 are best known for their anti-inflammatory properties. KBA and AKBA have been shown to inhibit 5-lipoxygenase and subsequent leukotriene production,

inhibit nuclear factor kappa B activation, inhibit human leukocyte elastase, and inhibit tumor necrosis factor alpha (TNF- α).^{26,27} Furthermore, *Boswellia* has also been shown to inhibit growth and invasion of glioma and additional tumor cells. It is thought that the antitumor properties are related to various biomarkers linked to inflammation. Overall, these actions result in a multimodal anti-inflammatory effect.

Several clinical trials have shown positive effects of *Boswellia* in inflammatory conditions.^{28,29}

A systematic review by Ernst et al identified 7 clinical trials evaluating the effects of *Boswellia* in asthma,³⁰ rheumatoid arthritis,³¹ Crohn's disease,³² and collagenous colitis.^{33,34} The majority of these studies lacked solid methodological quality. However, overall the results appeared encouraging. Additional clinical trials have investigated the use of *Boswellia* in osteoarthritis of the knee.³⁵ These, too, showed positive effect. While these studies show positive trends, additional clinical trials are certainly warranted and needed to solidify *Boswellia*'s place in treating inflammatory conditions.

Clinical trials evaluating the use of *Boswellia* in radiochemotherapy-associated cerebral edema do exist and show promise, but are few. These studies have evaluated the use of *Boswellia* in the form of H15. This is a standardized *Boswellia* extract from Germany containing only *Boswellia serrata* (BS) with AKBA and KBA in relative concentrations.³⁶ A 2001 study by Streffer et al investigated the use of H15 in 12 patients with cerebral edema.³⁷ Clinical or radiological response was found in 8 out of 12 patients. A small prospective study by Boeker et al found similar results.³⁸

The first randomized controlled pilot study evaluating *Boswellia* and its effects in cerebral edema came from Kirste et al in 2010.⁴⁰ Patients with edema as a result of brain tumor irradiation experienced a reduction of cerebral edema >75% in 60% of the patients receiving BS (H15); a reduction of edema was also experienced in 26% of those in the placebo group. The primary adverse event in those receiving BS was diarrhea grades 1-2 (6 patients). The placebo group had 1 patient with grade 3 nausea and another with an epileptic seizure at a grade of 4. Per this and previous studies, the toxicity profile of boswellic acids is considered excellent.

Cerebral edema is caused by cellular damage, release of cytokines, and aberrant sodium transport, among other processes.¹⁸ It, therefore, makes sense, given the inflammatory nature of this phenomenon, that *Boswellia* may offer significant benefit in its prevention and management. Furthermore, boswellic acids have been shown to induce apoptosis of glioma cells and do not interfere with drug or radiation sensitivity.³⁹

The enteral absorption and subsequent bioavailability of *Boswellia* are questionable. Past studies have shown that oral *Boswellia* administration of 3,000 mg/day provides plasma concentrations that may be below pharmacologically active levels.⁴⁰⁻⁴² The Kirste et al study evaluated the absorption of H15 (the previously mentioned standardized concentration of *Boswellia*).⁴⁰ Plasma concentrations of KBA were, on average, 34.23 ng/mL, with AKBA present in lower concentrations of 2.83 ng/mL. These concentrations are low considering all patients in that study received 4,200 mg/day in divided doses (3 capsules 4 times daily). Of note, the patient with the

highest plasma KBA levels (123.1 ng/mL with a range of 53.25-153.49 ng/mL) had the largest observed reduction in edema from baseline to post radiotherapy.

Previous studies show that oral administration of phospholipid-based boswellic-acid formulations offers improved bioavailability. This type of composition exploits a steady state dispersion of boswellic acids into phospholipids.⁴³ Plausibly, this allows for greater enteral absorption. In an animal preclinical study, significantly increased concentrations of BS were observed in the liposomal delivery group of *Boswellia* compared to nonliposomal forms at the same dose. The maximum concentration (C_{max}) was 20-100 times higher compared to the standard/nonphospholipid BS extract, and the brain concentration of AKBA in these animals increased by 35-fold.⁴⁴ Quicker absorption and a significantly higher concentration of boswellic acids were also observed in a randomized crossover study on 12 healthy human volunteers.⁴⁷ This higher concentration was observed both in terms of weight-to-weight and molar comparisons. Unfortunately, brain concentrations were not measured in this trial.

The study reviewed here by Di Pierro and colleagues is the first clinical trial to evaluate an oral liposomal form of *Boswellia* in management of radiochemotherapy-induced cerebral edema. The *Boswellia* supplement was formulated by using a ratio of 1:1 *Boswellia serrata* extract (AKBA and KBA) with phospholipids. The total daily dose was 4,500 mg/day in all subjects, which is similar to previous studies.^{40,41} There is no mention of whether this dose was administered incrementally, although given the number of capsules, this may be assumed. Boswellic acids have been shown to reach a peak at 1-2 hours post oral ingestion and plateau approximately 2 hours later.²⁶ Therefore, *Boswellia* is likely best dosed multiple times throughout the day to offer a consistent therapeutic effect. Furthermore, divided doses may also help to ease and prevent gastrointestinal side effects from taking too much of the herb at once. (As noted, grade 1-2 diarrhea was the most common reaction in clinical trials so far.)

While the Di Pierro study holds promise and liposomal *Boswellia* may effectively manage, mitigate, and potentially prevent radiochemotherapy-induced cerebral edema, it is difficult to extrapolate data and effects of liposomal *Boswellia* conclusively. This largely stems from the fact that this was a small, nonrandomized, nonblinded, nonplacebo-controlled longitudinal pilot study. There was no assessment of plasma or brain concentrations of boswellic acids, making the evaluation of bioavailability unknown. Furthermore, there was no control group nor a separate, nonliposomal *Boswellia* group for comparison. Ideally, future studies would not only evaluate these concentrations but also determine the most appropriate plasma and brain concentrations that yield greatest therapeutic effect. These doses will likely differ based on body mass and individual enteral absorption. Additionally, these concentrations may correlate with the absolute need for dexamethasone. The need for future studies is substantial.

Given the known actions of *Boswellia* and clinical data so far, ideas for future studies are numerous. Ultimately, the best form of *Boswellia* administration may occur via bypassing oral delivery all together via parenteral administration and safe formulation of the specific, most active boswellic components. Additional properties of *Boswellia* should be assessed in terms of its radiosensitivity and cytotoxic potential. Furthermore, might *Boswellia* be synergistic with other therapies, both natural and pharmaceutical? For example, curcumin,⁴⁵⁻⁴⁸ metformin,^{49,50} melatonin,⁵¹⁻⁵³ and use of a ketogenic diet,⁵⁴⁻⁵⁷ among other treatments, are all examples of

therapies offering promise in the management of glioblastoma. It goes without saying that any combination must conclusively augment standard of care without compromising its effects.

Given the disastrous nature of radiochemotherapy-induced cerebral edema, its ability to compromise effective standard of care, and the less-than-desirable standard therapies used in its mitigation, *Boswellia* is intriguing. Its largest drawback may be its limited absorption. Despite this fact, previous studies utilizing less-than-optimal therapeutic concentrations still show benefit.^{32,40,41} What additional benefits might we find and how might we best help our patients if we can leverage this herb to its greatest potential? The future will yield these answers. In the meantime, the present use of *Boswellia* appears safe and favorable in those patients undergoing standard treatment for GBM.

About the Author



Kirsten West, ND, LAc, FABNO, is a graduate of Southwest College of Naturopathic Medicine and Health. She completed a naturopathic oncology residency at Cancer Treatment Centers of America in Philadelphia. West earned her undergraduate degree at University of Colorado in Boulder and completed her masters in Acupuncture at The Colorado School of Chinese Medicine. Since graduating with her medical degree in 2009, she has worked with University of Colorado Hospital's Integrative Wellness center to facilitate internships for medical students interested in integrative medicine and continues to foster relationships with the conventional and integrative oncology world at large. West is membership chair for the Oncology Association of Naturopathic Physicians (OncANP), was an executive officer and founding member of the Naturopathic Post Graduate Association. She maintains an integrative oncology practice in Boulder, Colorado.

References

1. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee ShU. Glioblastoma multiforme: a review of its epidemiology and pathogenesis through clinical presentation and treatment. *Asian Pac J Cancer Prev*. 2017;18(1):3-9.
2. Thurnher MM. 2007 World Health Organization classification of tumours of the central nervous system. *Cancer Imaging*. 2009;9 Spec No A(Special issue A):S1-3.
3. Tykocki T, Eltayeb M. Ten-year survival in glioblastoma: a systematic review. *J Clin Neurosci*. 2018;54:7-13.
4. Cote DJ, Ostrom QT, Gittleman H, et al. Glioma incidence and survival variations by county-level socioeconomic measures. *Cancer*. 2019;125(19):3390-3400.
5. Udaka YT, Packer RJ. Pediatric brain tumors. *Neurol Clin*. 2018;36(3):533-556.
6. Subramanian S, Ahmad T. Cancer, childhood brain tumors. [Updated 2019 Nov 12.] In: tkStatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; January 2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK535415/>.
7. Amirian ES, Zhou R, Wrensch MR, et al. Approaching a scientific consensus on the association between allergies and glioma risk: a report from the glioma international case-control study. *Cancer Epidemiol Biomarkers Prev*. 2016;25(2):282-290.

8. Daugherty SE, Moore SC, Pfeiffer RM, et al. Nonsteroidal anti-inflammatory drugs and glioma in the NIH-AARP Diet and Health Study cohort. *Cancer Prev Res (Phila)*. 2011;4(12):2027-2034.
9. Miller AB, Sears ME, Morgan LL, et al. Risks to health and well-being from radio-frequency radiation emitted by cell phones and other wireless devices. *Front Public Health*. 2019;7:223.
10. Carlberg M, Hardell L. Decreased survival of glioma patients with astrocytoma grade IV (glioblastoma multiforme) associated with long-term use of mobile and cordless phones. *Int J Environ Res Public Health*. 2014;11(10):10790-10805.
11. Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. *JAMA*. 2015;314:2535-2543.
12. Fernandes C, Costa A, Osório L, et al. Current standards of care in glioblastoma therapy. In: De Vleeschouwer S, editor. *Glioblastoma* [Internet]. Brisbane, AUtk: Codon Publications; September 27, 2017. Chapter 11.
13. Mann J, Ramakrishna R, Magge R, Wernicke AG. Advances in radiotherapy for glioblastoma. *Front Neurol*. 2018;8:748.
14. Walker MD, Green SB, Byar DP, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med*. 1980;303:1323-1329.
15. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *The Lancet Oncology*. 2009;10(5):459-466.
16. Lin ZX. Glioma-related edema: new insight into molecular mechanisms and their clinical implications. *Chin J Cancer*. 2013;32(1):49-52.
17. Gensler LS. Glucocorticoids: complications to anticipate and prevent. *Neurohospitalist*. 2013;3(2):92-97.
18. Pitter KL, Tamagno I, Alikhanyan K, et al. Corticosteroids compromise survival in glioblastoma. *Brain*. 2016;139(5):1458-1471.
19. Evans ML, Graham MM, Mahler PA, Rasey JS. Use of steroids to suppress vascular response to radiation. *Int J Radiat Oncol Biol Phys*. 1987;13(4):563-567.
20. Weller M, Schmidt C, Roth W, Dichgans J. Chemotherapy of human malignant glioma: prevention of efficacy by dexamethasone? *Neurology*. 1997;48(6):1704-1709.
21. Schneider H, Weller M. Boswellic acid activity against glioblastoma stem-like cells. *Oncol Lett*. 2016;11(6):4187-4192.
22. Swanson KD, Lok E, Wong ET. An overview of alternating electric fields therapy (novoTTF therapy) for the treatment of malignant glioma. *Curr Neurol Neurosci Rep*. 2016;16(1):8.
23. Reising K, Meins J, Bastian B, et al. Determination of boswellic acids in brain and plasma by high-performance liquid chromatography/tandem mass spectrometry. *Anal Chem*. 2005;77(20):6640-6645.
24. Siddiqui MZ. *Boswellia serrata*, a potential antiinflammatory agent: an overview. *Indian J Pharm Sci*. 2011;73(3):255-261.
25. Banno N, Akihisa T, Yasukawa K, et al. Anti-inflammatory activities of the triterpene acids from the resin of *Boswellia carteri*. *J Ethnopharmacol*. 2006;107(2):249-253.

26. Krüger P, Daneshfar R, Eckert GP, et al. Metabolism of boswellic acids in vitro and in vivo. *Drug Metab Dispos.* 2008;36(6):1135-1142.
27. Poeckel D, Werz O. Boswellic acids: biological actions and molecular targets. *Curr Med Chem.* 2006;13(28):3359-3369.
28. Ernst E. Frankincense: systematic review. *BMJ.* 2008;337:a2813.
29. Ammon HP. Boswellic acids in chronic inflammatory diseases. *Planta Med.* 2006;72(12):1100-1116.
30. Gupta I, Gupta V, Parihar A, et al. Effects of *Boswellia serrata* gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. *Eur J Med Res.* 1998;3(11):511-514.
31. Sander O, Herborn G, Rau R. [Is H15 (resin extract of *Boswellia serrata*, “incense”) a useful supplement to established drug therapy of chronic polyarthritis? Results of a double-blind pilot study]. *Z Rheumatol.* 1998;57(1):11-16.
32. Gerhardt H, Seifert F, Buvari P, Vogelsang H, Repges R. [Therapy of active Crohn disease with *Boswellia serrata* extract H 15]. *Z Gastroenterol.* 2001;39(1):11-17.
33. Madisch A, Miehlke S, Eichele O, et al. *Boswellia serrata* extract for the treatment of collagenous colitis: a double-blind, randomized, placebo-controlled, multicenter trial. *Int J Colorectal Dis.* 2007;22(12):1445-1451.
34. Sontakke S, Thawani V, Pimpalkhute S, Kabra P, Babhulkar S, Hingorani L. Open, randomized, controlled clinical trial of *Boswellia serrata* extract as compared to valdecoxib in osteoarthritis of knee. *Indian J Pharmacol.* 2007;39:27-9.
35. Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee—a randomized double blind placebo controlled trial. *Phytomedicine.* 2003;10(1):3-7.
36. Kirste S, Treier M, Wehrle SJ, et al. *Boswellia serrata* acts on cerebral edema in patients irradiated for brain tumors: a prospective, randomized, placebo-controlled, double-blind pilot trial. *Cancer.* 2011;117(16):3788-3795.
37. Streffer JR, Bitzer M, Schabet M, Dichgans J, Weller M. Response of radiochemotherapy-associated cerebral edema to a phytotherapeutic agent, H15. *Neurology.* 2001;56(9):1219-1221.
38. Boeker DK, Winking M. The role of boswellic acids in therapy of malignant glioma. *Dt Aertzebl.* 1997;94:1197-1199.
39. Glaser T, Winter S, Groscurth P, et al. Boswellic acids and malignant glioma: induction of apoptosis but no modulation of drug sensitivity. *Br J Cancer.* 1999;80(5-6):756-765.
40. Du Z, Liu Z, Ning Z, et al. Prospects of boswellic acids as potential pharmaceuticals. *Planta Med.* 2015;81(4):259-271.
41. Riva A, Morazzoni P, Artaria C, et al. A single-dose, randomized, cross-over, two-way, open-label study for comparing the absorption of boswellic acids and its lecithin formulation. *Phytomedicine.* 2016;23(12):1375-1382.
42. Abdel-Tawab M, Werz O, Schubert-Zsilavec M. *Boswellia serrata*: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet.* 2011;50(6):349-369.
43. Matias D, Rijo P, Reis CP. Phytosomes as biocompatible carriers of natural drugs. *Curr Med Chem.* 2017;24(6):568-589.
44. Hüsch J, Bohnet J, Fricker G, et al. Enhanced absorption of boswellic acids by a lecithin delivery form (Phytosome®) of *Boswellia* extract. *Fitoterapia.* 2013;84:89-98.

45. Klinger NV, Mittal S. Therapeutic potential of curcumin for the treatment of brain tumors. *Oxid Med Cell Longev*. 2016;2016:9324085.
46. Del Prado-Audelo ML, Caballero-Florán IH, Meza-Toledo JA, et al. Formulations of curcumin nanoparticles for brain diseases. *Biomolecules*. 2019;9(2):56.
47. Leng L, Zhong X, Sun G, Qiu W, Shi L. Demethoxycurcumin was superior to temozolomide in the inhibition of the growth of glioblastoma stem cells in vivo. *Tumour Biol*. 2016;37(12):15847-15857.
48. Yin H, Zhou Y, Wen C, et al. Curcumin sensitizes glioblastoma to temozolomide by simultaneously generating ROS and disrupting AKT/mTOR signaling. *Oncol Rep*. 2014;32(4):1610-1616.
49. Valtorta S, Lo Dico A, Raccagni I, et al. Metformin and temozolomide, a synergic option to overcome resistance in glioblastoma multiforme models. *Oncotarget*. 2017;8(68):113090-113104.
50. Seliger C, Lubber C, Gerken M, et al. Use of metformin and survival of patients with high-grade glioma. *Int J Cancer*. 2019;144(2):273-280.
51. Lissoni P, Meregalli S, Nosetto L, et al. Increased survival time in brain glioblastomas by a radioneuroendocrine strategy with radiotherapy plus melatonin compared to radiotherapy alone. *Oncology*. 1996;53(1):43-46.
52. Maitra S, Bhattacharya D, Das S, Bhattacharya S. Melatonin and its anti-glioma functions: a comprehensive review. *Rev Neurosci*. 2019;30(5):527-541.
53. Reiter RJ, Rosales-Corral SA, Tan DX, et al. Melatonin, a full service anti-cancer agent: inhibition of initiation, progression and metastasis. *Int J Mol Sci*. 2017;18(4):843.
54. van der Louw EJTM, Olieman JF, van den Bemt PMLA, et al. Ketogenic diet treatment as adjuvant to standard treatment of glioblastoma multiforme: a feasibility and safety study. *Ther Adv Med Oncol*. 2019;11:1758835919853958.
55. Maroon J, Bost J, Amos A, Zuccoli G. Restricted calorie ketogenic diet for the treatment of glioblastoma multiforme. *J Child Neurol*. 2013;28(8):1002-1008.
56. Schwartz K, Chang HT, Nikolai M, et al. Treatment of glioma patients with ketogenic diets: report of two cases treated with an IRB-approved energy-restricted ketogenic diet protocol and review of the literature. *Cancer Metab*. 2015;3:3.
57. Mukherjee P, Abate LE, Seyfried TN. Antiangiogenic and proapoptotic effects of dietary restriction on experimental mouse and human brain tumors. *Clin Cancer Res*. 2004;10(16):5622-5629.