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Original Research Article (Clinical)

Effects of *Raupya Suvarna Sutashekhara*, a herbo-mineral-metallic formulation as adjunct Oral Ayurvedic Medicine on long-term survival in patients of malignant brain tumor

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ABSTRACT

Background: The incidence of brain tumors poses a significant threat, particularly with high-grade tumors that exhibit rapid growth and can significantly impair the patient's quality of life, despite treatment modalities. Ayurveda, a natural system of medicines helps to enhance health benefits when used as a complementary therapy in combination with conventional treatment through various herbal, herbo-mineral or herbo-mineral-metallic formulations. One of such formulations, *Raupya Suvarna Sutshekhara (RSS),* has *Raupya bhasma* and *Suvarna bhasma* (incinerated Silver and Gold respectively) ingredients and they are described as *Rasayana* (immuno-modulatory) and possess *Medhya* (enhances the brain functions and intelligence) activity.

Objective: The study documents effects of *Raupya Suvarna Sutshekhara* in alleviating symptoms of malignant brain tumors.

Materials and methods: This retrospective cohort study was done for malignant brain tumor patients (n = 110) registered at our centre who were treated with *Raupya Suvarna Sutshekhara* 125 mg–250 mg (a herbo-mineral metallic formulation) as a treatment of choice of neural tonic along with supporting Ayurvedic medicines. Treatment response evaluation period ranged from 3 months to 5 years (median period 29 weeks). Clinical symptoms, weight, Karnofsky Performance Score (KPS), Quality of Life (QoL) score, and survival data with respect to treatment with RSS were analyzed.

Results: RSS showed a very significant ($p < 0.001$) effect on symptoms related to memory loss, headache, imbalance, loss of appetite, and generalized weakness while significant ($p < 0.05$) decrease in urinary incontinence, seizures, difficulty in thinking/articulating, and weakness in one part/side of the body. However, a not-quite significant change was seen in symptom confusion/disorientation. No significant improvement was seen in vision changes, facial numbness or tingling, swallowing difficulties, and tingling in extremities. Body weight and KPS also showed improvement. Patients with treatment between 2 and 5 years showed median survival up to 62 months.

Conclusions: It was observed that adjunct Ayurvedic treatment with RSS helped to reduce the severity of symptoms due to the tumor itself or side-effects of conventional treatments, maintain the quality of life of malignant brain tumor patients and has shown to increase survival with respect to the duration of the treatment.

1. Introduction

Amongst all types of cancer in adults, malignant brain tumors are rare accounting for 1–2% [1]. Brain and other nervous system cancer, ranked 10th leading cause worldwide, constitute 85–90% of all primary central nervous system (CNS) tumors. Approximately 308,102 people

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were diagnosed with a primary brain or spinal cord tumor in 2020 [2]. According to GLOBOCAN 2022, the incidence of malignant brain tumors worldwide was 2.8% in males and 1.7% in females while the mortality was 3.1 [3] In India, 2.3% of new cases are seen ranking 19th among all cancers and 12th in mortality rate [4]. The survival rate of malignant brain tumors is 35.6% wherein the survival of Glioblastoma, a common form of primary brain tumor, is only 6.9% with its median survival about 8 months only [5]. Despite aggressive treatment, including extensive surgery, concurrent radiation, and adjuvant temozolomide, the median survival time of adult patients typically hovers around 10 months. However, in cases where combined treatment with radiotherapy is administered, the median survival time may extend up to 14 months [6].

Brain tumors are classified into low grade (Grade I and II) and high grade (Grade III and IV) by World Health Organization. Survival of brain tumor patients depends on type and age of the patient. Though low-grade glioma patients have better survival rates compared to patients with high-grade glioma, all low-grade gliomas are invasive and eventually progress to high-grade glioma leading to death [7]. Despite the availability of treatment options such as surgery, radiation with concurrent chemotherapy, the prognosis remains poor, with high-grade tumor patients having an overall survival of only 14 months [8]. This is primarily due to the resistance of glioblastoma multiforme (GBM) cells, which evade conventional treatments by resisting cell death and rapidly regenerating cancer cells. Additionally, the blood-brain barrier poses a challenge by limiting the effectiveness of chemotherapy through hindering drug delivery to GBM cells. In spite of these challenges, emerging treatments include immunotherapy (checkpoint inhibitors), and targeted therapies (bevacizumab), that attempt to attack specific vulnerabilities in GBM cells. Additionally, the use of tumor-treating fields, a type of electric field therapy that has been shown to slow the growth of GBM cells. Ongoing clinical trials are assessing the safety and efficacy of these innovative treatments, with the aim of improving outcomes for GBM patients [9].

Ayurveda, an ancient system of medicine advocates the primary goal of maintaining health of healthy and curing diseases when suffering from ill health [10]. It includes treatment modalities like *Shodhana* (detoxifying treatment), *Shamana* (pacifying treatment), and *Rasayana* (immunomodulatory treatment). The goal of improving health is achieved by the use of herbal, mineral, and elemental preparations in the treatment of diseases. *Raupya Suvarna Sutashekhara*, a proprietary herbo-mineral-metallic combination, majorly containing incinerated gold and silver, indicated in patients with hypertension, hysteria, epileptic convulsions, stroke, ulcerative colitis, hyperemesis [11].

The majority of pre-clinical research works are reported for use of herbal medicines in brain cancer. Among them, one of the review studies stated that, comprehensive analysis of characteristics of registered clinical trials related to herbal medicines and cancer, however, very few trials are registered for brain cancer [12]. Another study regarding the use of the curcumin in the cancer indicate that clinical trials should be undertaken to corroborate the benefits of curcumin seen in preclinical studies and improve the prognoses of individuals with brain tumors [13]. One of the case studies was carried out in the GBM patient, which include the intake of herbal preparation for 48 months, there were no clinical or radiological signs of the disease, in three patients; in one patient, the tumor was reduced and his condition was stable, and one patient lived for 48 months in spite of a large primary tumor and a massive recurrence, which developed after the treatment had been completed [14].

Considering this literature review and poor prognosis of the disease, additional/adjuvant complimentary therapy is also required to achieve the good quality of life and prolonged survival in brain cancer patient. Since many years, in our centre, herbo-mineral-metallic formulation, known as *Raupya Suvarna Sutshekhara* was administered to malignant brain tumor patients and found to be effective in prolonged survival of the patients. Hence, we have analyzed the data retrospectively to find out the effect of RSS to reduce the side of effects of the conventional treatment as well as to improve the quality of life and survival of the malignant brain cancer patients.

2. Materials and methods

2.1. Study design

This is a retrospective cohort study to analyze the effect of the RSS on the glioma. Patients at our clinic had received RSS ranging from 3 months to 5 years (median treatment period: 29 weeks). These cases were divided into 4 groups based on the duration of administration of RSS to glioma patients viz., Group 1 received the RSS for 12–24 weeks, Group 2 received for 25–52 weeks while Group 3 received for 1 year to 2 years, and Group 4 – more than 2 years up-to 5 years. The data regarding demographic, conventional and Ayurvedic treatment details, radiological, mutational analysis, pathological investigations was obtained from the case record form filled at the time of registration and followed-up subsequently. There were no major modifications in the case record form. The patients having symptoms like headache, seizures/convulsions, difficulty in thinking or speaking or articulating, weakness/paralysis in one part or one side of the body, loss of balance/dizziness, vision changes, facial numbness or tingling, nausea or vomiting, swallowing difficulties, confusion/disorientation, loss of appetite, memory loss, urine incontinence, constipation, tremors/tingling sensation in extremities, sleep disturbances, generalized weakness/muscle weakness, lack of concentration, and lethargy etc. were graded as per Common Terminology Criteria for Adverse Event (CTCAE) version 4.03 (Grading of symptoms on 0 to 4 scales) and analyzed. The study was approved in institutional ethics committee meeting held on Aug 4, 2006.

Inclusion – exclusion criteria:

The malignant brain tumor (Glioma) patients registered between 1995 and 2021 were enrolled in the study. The patients aged between 4 and 70 years (median age 40 years) of both genders, high or low grade, who have under or completed the conventional treatment viz. surgery, chemotherapy, radiotherapy was included. The patients who have taken RSS for less than 3 months were excluded from the study.

2.2. Treatment protocol

Considering the nature of brain tumors and the treatment-induced symptoms, RSS was administered in a dose of 125 mg once or twice a day to all the patients. Along with RSS, other formulations like *Mauktik Kamdudha vati* (MKD) 250–500 mg, *Liv Atharva* 10 ml, *Pippalyasava* 10 ml twice a day after meals were also given. *Jatamansi Taila* was given as an external application in the form of *Shiropichu* (placing oil-soaked cotton gauze on the head) at night before bedtime (Table 1).

2.3. Outcome measures

The outcome of the study was analyzed by Clinical symptoms, Body weight, Karnofsky Perfoemance Score (KPS), Quality of Life score (C-30 of EORTC (European Organization for Research and Treatment of Cancer) [15], and survival data with respect to starting and completion of the treatment with RSS. Overall survival period after starting OAM was calculated from the date of registration until death or last follow-up. Karnofsky score ranges from 0 to 100, a higher score denotes a better ability to carry out daily activities [16]. QLQ C-30 was determined by patients' own perspective about his/her own well-being and interpreted as functional score, symptom score, and global score. A higher score on functional and global scales interprets the high functional level and quality of life while a lower symptom scale represents the lower level of symptomatology.

2.4. Statistical analysis

The data were entered and stored in Microsoft Excel 2019 and

Table 1
A detailed description of RSS and other formulations used in the glioma patients.

Sr. No.	Name of the medicine	Contents	Properties as per Ayurvedic texts	Mode of action in patients	Reported pharmacological Actions
1.	*Raupya Suvarna Sutashekhar Rasa*	*Raupya Bhasma* (incinerated silver), *Suvarna Bhasma* (incinerated gold), *Kajjali* (black sulphide of mercury), *Tamra Bhasma* (incinerated copper), *Shankha Bhasma* (incinerated conch), Processed Tankan (purified borax powder) **Herbs**-*Shunthi* root (*Zinziber officinale*), *Marich* fruit (*Piper nigrum*), *Pippali* fruit (*Piper longum*), *Twak* bark (*Cinnamomum zeylanicum*), *Ela* pods (*Elettaria cardamomum*), *Tamalpatra* leaf (*Cinnamomum zeylanicum*), *Nagkeshar* stamens (*Me\sua ferrea*), *Kachora* root (*Hedychium spicatum*), Processed *Vatsanabh* root (*Aconitum ferox*), Processed *Dhattura* seed (*Dhatura stramonium*), and *Bilva* Unripe fruit pulp (*Aegle marmelos*) all in equal proportion triturated with fresh juice of *Bhringaraj* (*Eclipta alba*) whole plant.	***Raupya-Suvarna Bhasma*** Best in scraping of unwanted vitiated *Dhatu* (*Paramlekhana*), improving strength, stamina, and immunity, cardiotonic, improving intelligence, prolonging young age, Improving metabolic fire. [25, 16/46–51, 15/69–80] ***Kajjali***- *Yogavahi* (carrier of qualities of other components) [25, 6/112] ***Shankha bhasma***- reduces Hyperacidity, *Grahi* (absorptive), *Vishagna* (removes toxins) [25, 12/21] **Herbs**: Improve metabolic fire, digestion and absorptive, used in Brain related disorders (*Shirortinut*). [38, 2/63, 3/63, 3/100, 4/241] ***Visha dravya***: Increases blood circulation, worm manifestation	• Reduce pain, nausea, vomiting in patients. • Pacifying action on the nerves. • Improve immunity, digestion and metabolism.	Antitoxin, immunomodulator, nootropic, antirheumatic, antimicrobial, antiviral, and a tonic for the nervous system. [27] Anxiolytic effect [28] Analgesic, anti-inflammatory, anti-anxiety, cognitive, antidepressant, neuroleptic, and antiepileptic effects on the body [26]
2.	*Mauktik Kamduddha*	*Shankha bhasma* (Incinerated Conch) *Kapardika bhasma*, (Incinerated Cowry) *Mukta-shukti bhasma* (Incinerated Pearl oyster) *Pravala bhasma* (Incinerated Coral) *Suvarnagairik* (Purified ochre) *Guduchi satva* (Starch from *Tinospora cordifolia*)	*Kamduddha* rasa is cold in potency (*Sheeta veerya*), effective on the digestive system, circulation, nervous system, and urinary system, alleviates *pitta dosha* (*Pittashamana*), Anti-pyretic (*Jwaraghna*) Beneficial in *Amlapitta*, dizziness (*Bhrama*), and mental disturbance (*Unmada*), and reduces body heat (*Dahashamana*), balances acid production in the stomach, reduces inflammation of the organs of the digestive system, and lowers the tendency of bleeding.	• Minimize side effects of chemotherapy and help to reduce toxins accumulated in the body. • Reduce body heat and inflammation of the digestive system. • Improve digestion.	Incinerated minerals containing Calcium carbonate reduce heartburn by significantly improving peristalsis movement and acid clearance [39].
3.	Liv Atharva Liquid	*Kumari swaras* (*Aloe vera*), *Dhataki* (*Woodfordia fruticosa*) *Haridra* (*Curcuma longa*), *Pippali* (*Piper longum*), *Vidanga* (*Emblica ribes*) *Haritaki* (*Terminalia chebula*), Guda (Jaggery) etc.		• Useful in Liver disorders, chemotherapy-induced sluggish liver. • Improves appetite & digestion. • Improves general health & resistance against cold and cough. • Helps to purify blood.	anti-inflammatory, analgesic, antioxidant, hepatoprotective properties [40–42]
4.	*Pippalyasava*	*Pippali* (*Piper longum*), *Haridra* (*Curcuma longa*), *Draksha* (*Vitis vinifera*), *Dhataki* (*Woodfordia fruticosa*), *Guda* (Jaggery) etc.	Depletion of *dhatu* (*Kshaya*), *Gulma,* ascites (*Udara*) emaciation (*Karshya*) *Grahani* anaemia (*Pandu*) Haemorrhoids (*Arsha*)	• Good for digestive system functions hampered due to chemotherapy. • Effective in functioning of liver and spleen. • Effective in treating chronic cough, cold, breathlessness.	anti-inflammatory, analgesic, anti-oxidant, hepatoprotective properties [25]

interpreted as Mean ± SEM (Standard Error Mean). The C-30 scores were linearly arranged between 0 and 100 scale by using the scoring manual. The difference in means of score and symptoms was compared by paired 't'-test using Instat software version 3.0. The $p < 0.05$ was considered significant.

3. Results

3.1. Demographic data

Among the 110 patients examined, the demographic distribution of data observed is mentioned in Table 2. Histopathological reports were not available for two patients, who were diagnosed as malignant based on Radiological imaging (Group 1, n = 1) and Group 2, n = 1) (Table 2). The majority of patients (n = 64, 58.18%) underwent surgery followed by radiation therapy (with a dose ranging from 5400 cGy to 6000 cGy over 25 to 33 fractions) and chemotherapy (either oral chemotherapy with Tab. Temozolomide for 6 to 24 cycles or intravenous chemotherapy). A single patient (0.90%) chose not to pursue any conventional therapy (Table 2).

In total, 83% of patients presented with glial cell tumor while only 6.36% with embryonal cell tumor in all the groups. In the Molecular analysis, only n = 36 patients' data were available for evaluation from the cohort, revealed that 47% of patients in Group 1 tested positive for both p53 and GFAP. In Group 2, 50% of patients were positive for GFAP and Mib-1 mutations. Within Group 3, 83.33% and 50% of patients were

Table 2
Demographic data of malignant brain tumor patients (n = 110)

Group		1	2	3	4
		No. of Patients (%)	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)
Sex	Male	31 (64.58)	20 (58.82)	13 (76.47)	7 (63.63)
	Female	17 (35.41)	14 (41.17)	4 (23.52)	4 (36.36)
Age (in years)	<16	4 (8.33)	4 (11.76)	4 (23.52)	2 (18.18)
	16–40	13 (11.81)	11 (10)	9 (8.18)	9 (8.18)
	41–60	19 (17.27)	16 (14.55)	3 (2.72)	0
	>60	12 (10.9)	3 (2.72)	1 (0.91)	0
Grade	I	1 (2.08)	1 (2.94)	0	0
	II	9 (18.75)	3 (8.82)	4 (23.52)	3 (27.27)
	III	9 (18.75)	9 (26.47)	6 (35.29)	6 (54.54)
	IV	27 (56.25)	20 (5.88)	7 (41.17)	2 (4.16)
	Not Known	2 (4.16)	1 (2.94)	0	0
Type of tumour	Glial cell tumors[b]	38 (79.16)	30 (88.23)	12 (70.58)	11 (100)
	Embryonal tumors[c]	2 (4.17)	2 (5.88)	3 (17.64)	0
	Tumors of pineal region[d]	0	0	1 (5.88)	0
	Ependymoma	0	1 (2.94)	0	0
	Meningioma	2 (4.17)	0	1 (5.88)	0
	DNA	6 (12.5)	1 (2.94)	0	0
Conventional treatment	Only SU	2 (1.81)	0	0	0
	Only RT	5 (4.54)	1 (0.9)	0	1(0.9)
	SU + RT	14 (12.72)	6 (5.45)	3 (2.72)	5 (4.54)
	RT + CH	3 (2.72)	3 (2.72)	2 (1.81)	–
	SU + RT + C–CH	24 (21.81)	24 (21.81)	11 (10)	5 (4.54)
	No Treatment	0	0	1 (0.9)	0
Molecular analysis[a]	IDH 1/2 (R132H)	P-1 (6.66) N-2 (13.33)	P- 1 (8.33) N- 4 (33.33)	P- 1 (16.66)	P- 3 (75)
	1p/19q codeletion	N- 3 (20)	N- 2 (16.66)	-	P- 1 (25) N- 1 (25)
	1p deletion	P- 2 (13.33) N- 1 (6.66)	-	-	-
	19q deletion	-	P-1 (8.33)	-	-
	MGMT Promoter	N- 1 (6.66)	P- 1 (8.33)	P- 1 (16.66)	–
	ATRX loss on function	P- 3 (20) N- 1 (6.66)	P- 1 (8.33) N- 3 (25)	P- 1 (16.66)	P- 0 N- 2 (50)
	EGFR amplification	N- 1 (6.66)	–	–	P- 1 (25)
	Ki-67	N- 1 (6.66)	P- 1 (8.33)	P- 3 (50)	N- 1 (25)
	p53	P- 5 (33.33)	P- 8 (66.67) N- 1 (8.33)	P- 2 (33.33)	P- 2 (50)
	GFAP	P- 7 (46.66) N- 2 (13.33)	P- 6 (50) N- 1 (8.33)	P- 5 (83.33)	P- 1 (25)
	Mib-1	P- 10 (66.67) N- 1 (6.67)	P- 6 (50) N- 3 (25)	P- 2 (33.33) N- 2 (33.33)	P- 2 (50) N- 1 (25)

SU- Surgery, C–CH: Concurrent chemotherapy, RT- Radiotherapy, P-Positive, N-Negative, IDH: isocitrate dehydrogenase, MGMT: O^6-methylguanine-DNA-methyltransferase; ATRX-alpha-thalassemia/mental retardation, X-linked; EGFR-epidermal growth factor receptor; GFAP- glial fibrillary acidic protein.

[a] Out of 110 patients, n = 23- reports were not available for patients who were registered between 1995 and 2006, n = 36 -molecular analysis reports are available, while n = 51- molecular analysis were not done.

[b] Astrocytoma, Glioblastoma, Glioma, Oligoastrocytoma, Oligodendroglioma & Pontine Glioma.

[c] Medulloblastoma, Neuroblastoma.

[d] Pineoblastoma.

positive for GFAP and Ki67, respectively. Notably, all patients in Group 4 tested positive for IDH 1/2 (R132H) mutations, and 50% also showed p53 mutations (Table 2).

Out of 110 patients, (n = 54) 49% patients were not advised steroid while (n = 49) 44.5% of patients received steroid post-surgery or during RT in continuous or tapering dose. The majority of these patients were prescribed Dexamethasone with median dose of 4 mg (0.5–18 mg/day) or Prednisolone (5–200 mg/day). Among them, n = 21 (19.09%) patients had completed this course before starting Ayurvedic treatment while n = 27 (24.54%) patients were under steroid supplements in continuous or tapering dose during enrolment in the project. According to group classification, 25% of patients from group 1 received steroids before Ayurvedic treatment while 23% of patients were under steroidal dose. In group 2, 15% and 35% of patients received steroids before and during Ayurvedic treatment, respectively. However, 12% and 18% of patients from group 3 and 4, received steroids before and during Ayurvedic treatment, respectively. The median duration of steroid treatment was 3 weeks (Range: 5 days to 365 weeks) (Table 3a,b).

3.2. Symptom analysis of malignant brain tumor patients

The number of patients exhibiting particular symptoms and mean gradation before and after treatment with RSS is illustrated graphically and has been enlisted in Table 4.

Symptom analysis of patients showed an extremely significant improvement on headache, loss of balance/dizziness, nausea or vomiting, loss of appetite, memory loss, urine incontinence), constipation and generalized weakness while significant decrease was seen in seizures/convulsions, difficulty in thinking/articulating, weakness in one part/side. A not-quite significant change was seen in confusion/disorientation. Non-significant decrease was seen in vision changes, facial numbness or tingling, and tingling in extremities while non-significant increase in swallowing difficulties.

3.3. Clinical evaluation of quality of life

Body weight (n = 96) showed significant increase ($p = 0.04$) while Karnofsky's performance score ($n = 110$) was very significantly (p = 0.008) increase after the treatment (Table 5).

The functional scale items like physical, role, emotional, social and cognitive functioning was not statistically significant, while symptom

Table 3a
Use of steroids in brain cancer patients of all groups.

Groups	Yes	No/Not advised	DNA	Dexamethasone 4 mg/day (0.5–18 mg/day)	Prednisolone (5–200 mg/day)	DNA
1 (n=48)	25 (52.1)	21 (43.8)	2 (4.2)	18 (37.5)	3 (6.25)	4 (8.33)
2 (n=34)	15 (44.1)	14 (41.2)	5 (14.7)	12 (35.3)	2 (5.9)	1 (2.9)
3 (n=17)	05 (29.4)	12 (70.6)	0	04 (23.5)	1 (5.9)	0
4 (n=11)	04 (36.4)	07 (63.6)	0	03 (27.3)	1 (9.09)	0
Total	49 (44.54)	54 (49.09)	7 (6.36)	37 (33.63)	7 (6.36)	5 (4.54)

DNA: Data not available.

Table 3b
Dose of steroids (Dexamethasone/Prednisolone) w.r.t. Ayurvedic treatment.

Group	Before Ayurvedic treatment			During Ayurvedic treatment			DNA		
	Continuous	Tapering	DNA	Continuous	Tapering	DNA	Continuous	Tapering	DNA
1	3 (12)	8 (32)	1(4)	5 (20)	6 (24)	0	2 (8)	0	1(4)
2	0	4 (28.6)	1(7.1)	3 (21.4)	7 (50)	2 (14.3)	0	0	0
3	1(25)	1 (25)	0	0	2 (50)	0	0	0	0
4	2 (50)	0	0	1 (25)	1 (25)	0	0	0	0

DNA: Data not available.

Table 4
Distribution of malignant brain tumour patients and effect of Raupya Suvarna Sutshekhara (RSS) on clinical symptoms of malignant brain tumour patients.

	Symptoms	No. of patients (%)	Mean ± SE		*p*-value
			Before	After	
1.	Confusion/Disorientation	4 (3.6)	2.25 ±0.22	1.25 0.16	NS
2.	Constipation	12 (10.9)	1.92 ± 0.29	0.83 ± 0.21	0.005
3.	Difficulty Thinking, speaking or Articulating	29 (26.4)	1.72 ± 1.10	0.20 ± 0.13	0.01
4.	Facial Numbness or Tingling	5 (4.5)	1.40± 0.40	1.20 ± 0.20	NS
5.	Generalized weakness/ Muscle weakness	49 (44.5)	1.86 ± 0.11	1.43 ± 0.12	0.004
6.	Headaches	34 (30.9)	1.71 ± 0.16	1 ± 0.12	0.0007
7.	Lack of Concentration	7 (6.4)	0.57 ± 0.09	1.29 ± 0.15	NS
8.	Lethargy	5 (4.5)	1.40 ± 0.14	1.60 ± 0.14	NS
9.	Loss of Appetite	25 (22.7)	1.80 ± 0.15	1.16 ± 0.17	0.004
10.	Loss of Balance/dizziness	44 (40)	1.81 ± 0.14	1.22 ± 0.15	0.006
11.	Memory Loss	25 (22.7)	1.80 ± 0.19	1.20 ± 0.14	0.005
12.	Nausea or vomiting	16 (14.5)	1.44 ± 0.24	0.44 ± 0.16	0.008
13.	Seizures/Convulsions	8 (7.3)	1.38 ± 0.32	0.5 ± 0.19	0.05
14.	Sleep Disturbances	4 (3.6)	1.5 ± 0.15	1 ± 0.12	NS
15.	Stool Incontinence	2 (1.8)	2.5 ± 0.24	0.5 ± 0.07	NS
16.	Swallowing difficulties	2 (1.8)	0.67 ± 0.67	1.67 ± 0.33	NS
17.	Tremors/Tingling sensation in Extremities	14 (12.7)	1 ± 0.21	0.36 ± 0.37	NS
18.	Urine Incontinence	9 (8.2)	0.15 ± 0.05	0.07 ± 0.04	0.02
19.	Vision changes	15 (13.6)	1.67 ± 0.25	1.60 ± 0.19	NS
20.	Weakness/Paralysis in one part or one side of the body	44 (40)	1.93± 0.14	0.39 ± 0.12	0.04

Data presented in Mean ± SE, the difference in the mean of symptoms gradations were compared by using paired 't' test.

Table 5
Effect of RSS on Quality-of-Life scores, body weight, and Karnofsky Performance Score in malignant brain tumor patients

	Scale	Mean ± SE		*p*-value
Functional scale		**Before treatment**	**After treatment**	
	Physical Functioning	71.87 ± 2.62	69.39 ± 2.72	NS
	Role Functioning	67.77 ± 3.32	69.81 ± 2.84	NS
	Emotional Functioning	73.01 ± 2.01	72.51 ± 2.20	NS
	Cognitive Functioning	75.00 ± 2.39	74.84 ± 2.21	NS
	Social Functioning	72.64 ± 2.93	73.43 ± 2.84	NS
Symptoms scale	Fatigue	35.11 ± 2.44	34.59 ± 2.76	NS
	Nausea & Vomiting	8.65 ± 1.57	2.99 ± 0.97	0.001
	Pain	25.47 ± 2.49	20.60 ± 2.17	NS
	Dyspnoea	10.38 ± 2.16	8.81 ± 1.75	NS
	Insomnia	14.78 ± 2.45	16.04 ± 2.42	NS
	Appetite Loss	17.61 ± 2.69	16.98 ± 2.24	NS
	Constipation	16.35 ± 2.37	7.86 ± 1.64	0.01
	Diarrhoea	2.83 ± 1.19	1.89 ± 0.98	NS
	Financial Difficulties	38.36 ± 3.02	40.88 ± 3.14	NS
Global scale		52.75 ± 1.85	54.32 ± 2.14	NS
Body weight (n = 96)		59.37 ± 2.06	61.32 ± 1.84	0.05
Kernofsky performance score (n = 110)		72.82 ± 1.10	76.18 ± 1.42	0.01

Data presented in Mean ± SE, the difference in the mean scores were compared by using paired 't' test.

score was reduced indicating the improvement in the quality of life (n = 106). The global score also maintained after the treatment indicating general well-being (Table 5).

3.4. Survival analysis

The survival analysis was carried out based on the group and grade-wise classification with percentage of patients. Out of 110 patients, 21 patients (19.09%) survived between 3 and 6 months, 28 patients (25.45%) survived between 7 and 12 months, 29 patients (26.36%) between 13 and 24 months, 8 patients (7.27%) survived up to 36 months, 4 patients (3.63%) between 37 and 48 months, 6 patients (5.45%) survived up to 60 months, 3 patients (2.72%) up to 72 months, 4 patients (3.63%) up to 84 months, and 7 patients (6.36 %) survived for more than 96 months.

Out of a total of 110 patients, n = 87 (79.09%) of patients were diagnosed with high-grade tumors whose median survival was up to 18 months. Grade-wise survival of glioblastoma patients in all the groups are illustrated in Table 6 (a, b).

4. Discussion

Brain tumors can manifest in several ways. Firstly, the tumor's direct impact on specific brain regions can cause symptoms related to those areas. Secondly, as the tumor grows, it increases pressure inside the skull, leading to headaches. Depending on its location, seizures may also occur, with various types and severity, typically characterized by a focal onset and can be classified as simple partial, complex partial, or generalized seizures [8,17].

The standard conventional treatment protocol for brain tumors typically involves a combination of surgery, radiation, and chemotherapy. This therapeutic approach includes surgically removing or resecting the tumor, followed by radiation therapy and simultaneous adjuvant temozolomide (TMZ) treatment [18]. Additionally, patients with intracranial tumors often receive corticosteroids, particularly dexamethasone, as a routine measure to manage cerebral edema and alleviate symptoms. However, it's important to note that corticosteroid use may lead to systemic side effects, as well as gastrointestinal and neurological complications [19,20]. Primary brain tumors require a comprehensive, multi-modal treatment strategy. However, these treatments come with potential short-term and long-term side effects. Long-term effects may include central nervous system (CNS) focal and non-focal symptoms, complications in the peripheral nervous system, development of secondary neoplasms, and significant economic burden [21]. Short-term side effects may manifest as weakness, dizziness, impaired coordination or balance, confusion, speech difficulties, walking difficulties, weakness in extremities, impaired concentration or memory, behavioral changes, and speech problems. Additionally, radiotherapy can sometimes trigger headaches similar to migraines. Moreover, when combined with TMZ, side effects such as fatigue, nausea, vomiting, constipation, loss of appetite, and an increased risk of infections due to low blood counts are commonly experienced by patients [22,23].

Table 6

6a. Median Survival of Patients correlated with tumour grade and Overall Survival of patients

	Median Survival after starting RSS (in months)		Median overall survival (in months)	
	Grade III	Grade IV	Grade III	Grade IV
Group 1	6	6	33	12
Group 2	15	13	20	15.5
Group 3	17.5	22.5	37.5	35.5
Group 4	68.5	55	70.5	60

6b. Grade-wise survival analysis in glioblastoma patients of all the group

Group	Tumor grade	Median Survival (months)	Range (months)
Group 1	Grade I (n = 1)	96	–
	Grade II (n = 9)	8	3–67
	Grade III (n = 9)	6	3–57
	Grade IV (n = 27)	7	3–37
Group 2	Grade I (n = 1)	8	–
	Grade II (n = 3)	19	11–44
	Grade III (n = 9)	15	8–20
	Grade IV (n = 20)	13	7–61
Group 3	Grade I (n = 0)	–	–
	Grade II (n = 4)	34	15–71
	Grade III (n = 6)	19.5	14–60
	Grade IV (n = 7)	23.5	16–209
Group 4	Grade I (n = 0)	–	–
	Grade II (n = 2)	121	84–158
	Grade III (n = 6)	68.5	25–146
	Grade IV (n = 3)	76	34–240

Ayurveda has described *Shira* (brain) as *Uttamanga* (superior to all other body parts). Acharya Charak has mentioned *Ardhavabhedaka* (Migraine or Hemicrania) or headache, *Pratishyaya* (coryza), *Mukha, Nasika, Netra, Karna roga* (diseases of the oral cavity, nose, eye, and ear), *Bhrama* (dizziness), *Ardita* (facial palsy), *Shirokampa* (tremors in head), *Manya stambha* (Stiffness of neck), *Hanugraha* (lock jaw) etc. as symptoms seen due to aggravated *Vatadi doshas* [10]. Amongst the 107 *Marmas* (vital points) described in Ayurveda, *Shira* (brain)-*Hridaya* (Heart)-*Basti* (Urinary system) are the most important since the life of a human being depends on it. The *Dnyanendriyas* (special senses), *Karmendriyas* (organs involved in actions and important functions), and *Pranavaha srotasa* are associated with *Shira* just like the rays which radiate from the sun. These *Marmas* are to be protected from external injury or from imbalances in *Vatadi doshas* since they can destroy the body or cause very grave consequences. The following symptoms can manifest as a result of various conditions: *Manyastambha* (neck rigidity), *Ardita* (facial paralysis), *Chakshu-Vibhrama* (rolling of eyeballs), *Moha* (mental confusion), *Udveshtana* (cramps), *Chestanasha* (loss of function), *Kasa* (cough), *Svasa* (dyspnea), *Hanugraha* (lock-jaw), *Muka* (speechlessness), *Gadagada* (stammering), *Akshi-Nimilana* (ptosis), *Ganda-Spandana* (quivering of cheeks), *Jrimbhana* (yawning), *Lalasrava* (excessive salivation), *Svarahani* (voice loss), as well as diseases affecting the face and tongue [9, Siddhi Sthana, 9/3–6].

In ancient texts of Ayurveda, *Suvarna Sutshekhara rasa* (SS) has been described to relieve symptoms like *Chhardi* (vomiting), *Shoola* (pain), abdominal bloating, *Kasa* (cough), *Shwasa* (breathlessness), *Grahani* (colitis), *Agnimandya* (lack of appetite) and *Hikka* (hiccups). It also proves advantageous in *Rajyakshma* (a condition characterized by the wasting of different tissues, including *Rasa* and *Ojas*, resulting in immunodeficiency) [24].

Raupya Bhasma (incinerated silver) was added to this formulation considering its *Lekhana* (scraping of unwanted vitiated *dhatus*), *Rasayana* (immunomodulation) properties as *Medhya* (enhances the brain functions and intelligence) and rejuvenating the body. It is *Kashaya* (astringent) in taste with *Madhura vipaka* (resultant of metabolism), *Sheeta* (cool) in potency, *Sara* (mobile) *guna*, and pacifies *Vata* and *Pittadosha*. It is *Vayasthapaka* (anti-aging), *Balya* (strengthening), and *Hrudya* (cardioprotective). Due to its cooling action on the body, it reduces the burning sensation in the body, beneficial in *Trushna* (excessive thirst) and dryness of the mouth. It reduces dizziness and vomiting caused due to nervous excitement. It enhances appetite, as well as is beneficial in convulsions, heart disorders, and abdominal disorders [24, 16/46–51]. Incinerated silver has exhibited moderate analgesic activity against all types of noxious stimuli. Incinerated gold and silver have various central actions viz analgesic, anti-inflammatory, anti-anxiety, cognitive, antidepressant, neuroleptic, and antiepileptic effects on the body [26].

Suvarna Bhasma (incinerated gold) is *Madhura* (sweet) in taste, *Sheeta* (cold in potency), *Snigdha* (unctuous), *Rasayana* (immunomodulatory), *Vajikarana* (aphrodisiac), *Medhya* (improves intellect), *Hridya*

(cardiac tonic), *Balya* (strengthening), *Smritiprada* (improves memory), *Tridoshaghana* (alleviate all three *doshas*), *Yogavahi* (bioenhancer), *Chakshusya* (beneficial for the eyes), *Ojovridhhikara* (improves immunity), *Brimhana* (improves strength), etc. Overall, it acts on all organs in the body and improves their functions [24, 15/69–80]. *Suvarna Bhasma*, exhibits strong properties as an antitoxin, immunomodulator, nootropic, antirheumatic, antimicrobial, antiviral, and a tonic for the nervous system [27]. The anxiolytic effect has been seen in the zebrafish behavioral model which persisted even after the medicine was withdrawn [28]. It has been shown to exhibit antioxidants [29]. Calcine gold preparations have been found to reduce stress by lowering the effect of brain catecholamine, serotonin, and plasma corticosterone levels [30].

Tamra bhasma is *Tikta* (bitter), *Kashaya* (astringent), *Madhura rasa* (sweet), *Ushna veerya* (hot in potency), *Snigdha* (unctuous) having *Amla vipaka* (sour in resultant of metabolism). It is *pitta-kaphanashaka* (alleviates *Pitta* and *Kaphadosha*). It possesses *Vishanashaka* (eliminates toxins), *Lekhana* (scrapping action), *Deepana* (digestive) properties. It is beneficial in *Kasa* (cough), *Shwasa* (dyspnea), *Kshaya* (debility), *Pandu* (anemia), *Grahani* (colitis), *Netraroga* (eye disorders) and *Raktavikruti-janya vikara* (blood disorders) [24, 17/45–46]. It has shown to possess anti-oxidant properties [31].

Tankan (Borax) is *Katurasa* (Pungent) and *Ushna* (hot) in potency. It possesses *Tikshna* (penetrating), *Ruksha* (dry) and *Sara* (mobile) properties. It is beneficial for heart, Liver, and diseases like *Kasa* (cough), *Shwasa* (dyspnea), *Aadhmana* (flatulence) [24, 13/79–81].

Herbs like *Trikatu* (*P.longum, P. nigrum, Z. officinalis*); *Chaturjata* (*C. tamala*, *C. zeylanicum, E. cardamomum, M. ferrea*); Processed *Vishadravya* (*A. ferox, D. metel*) and fruit pulp of *A. marmelos*, and *H. spicatum* and juice of *E. alba* leaves used for trituration, are elaborated further and in Table 1.

Overall, the collective attributes of RSS suggest that it may possess *Katu-Tikta-Kashaya* rasa (pungent-bitter-astringent taste), *Ushna veerya* (hot in potency), *Madhura* or *Katu vipaka* (sweet or pungent post-digestive effect). Most of these are *Laghu* (light), *Ruksha* (dry), and *Tikshna* (penetrating) properties and have *Deepana-Pachana* (improve metabolic fire and digestion), *Shoolaghna* (analgesic), *Hridya* (cardiac tonic) and *Medhya* (improves intellect) action.

In the present study, we have observed that majority of patients are between 16-40 years and 41–60 years of age group. The reported literature also stated the incidence rate is higher at 41–60 years and up to 70 years [32].

Molecular features of glioblastoma are the tools for prognosis, risk stratification, or treatment decisions. These biological markers are genes, proteins, and other biological information that can provide details about brain tumors. The literary review regarding molecular analysis reported that large meta-analyses have shown that IDH mutations are associated with longer OS and PFS [33]. While p53 and Ki-67 proliferation index carries poor prognosis, or some studies concluded their prognostic value is uncertain [34,35]. while, in case of GFAP and Mib-1, prognostic relevance remains uncertain with conflicting results in multiple studies [36]. In the present study, majority of the patients were presented with IDH1/2(R132H), Ki-67, p53, GFAP and Mib-1 mutations. Amongst 36 patients, 12 patients from Group 1 having average overall survival of 33.25 months, 11 patients from Group 2 showed average overall survival of 33.77 months, 5 patients from Group 3 showed average overall survival of 43.2 months and 3 patients from Group 4 were diagnosed with high grade tumors having average overall survival of 61 months.

The symptoms like headache, nausea or vomiting, loss of appetite, weakness, loss of balance/dizziness, memory loss, and difficulty in thinking and articulating were the symptoms that showed significant positive differences after treatment with RSS. These symptoms are seen as a result of the presence of tumors or side effects of conventional treatment. According to Ayurveda, these symptoms are seen due to the vitiation of *Vata-Pitta doshas*. Headache is one of the predominant symptoms seen in brain tumors caused due to inflammation or as a side effect of the treatment. According to Ayurveda, *Shula* or pain is caused due to *Vata dosha* [37] which can be due to a depletion in the *dhatus* or obstruction in the passage of *Vata*. *Suvarna Sutshekhara* has a pacifying action in the body. This action is not that of reducing the sensation of pain but it alleviates the vitiated *doshas* for reducing the pain [27]. The *Deepana–Pachana* properties of ingredients in RSS has shown action in improving the appetite, which inhibit further *Aama* production.

The overall effect of RSS was seen in reducing symptoms viz., memory loss, dizziness, difficulty in thinking and articulating, headache, nausea or vomiting, loss of appetite, weakness, and loss of balance which showed a significant reduction of symptoms by treatment with RSS. The long-term administration of RSS was beneficial in controlling the growth of brain tumors without hampering sensory and motor actions of the brain. This effect of RSS is due to the cumulative effect of the ingredients of RSS. *Suvarna* and *Raupya bhasma* are *Medhya* and *Rasayana*, which act as neural tonics. *Raupya* and *Tamra bhasma* being *Lekhana* (scraping of unwanted vitiated *dhatu*) are beneficial to retard the growth of the brain tumor cells. Processed *Vatsanabha*, is useful in treating accumulated and vitiated blood in the brain or it helps in improving blood circulation and can cross the blood-brain barrier due to its *Vyavayi* and *Vikasi* (substances that spread quickly and act rapidly) actions. *Tankana* acts as an antidote for *Vatsanabha*, one of the *Vishadravya* (toxic drug). Processed *Dhattura*, apart from *Deepana* (improves metabolic fire), *Vishagna* (removes toxins) and *Krumighna* (evacuates worms), relives pain (head ache) caused due to brain tumor. Similar action is also exhibited by *Bhringaraja* [38]. *Shankha bhasma* is effective in hyperacidity and toxicities in the body. *Trikatu, Chaturjata, Bilvamajja* and *Kachora* help to improve metabolic fire and digestion which facilitates the easy absorption of the drug [38].

Along with this formulation, *Mauktik Kamdudha vati*, *Liv Atharva,* and *Pippalyadyasava* were also given after meals. These formulations have an effect on the digestive, respiratory, circulatory, and nervous system [27, 39]. The ingredients in these formulations possess anti-inflammatory, analgesic, antioxidant, and hepatoprotective properties [40–42]. The external application of *Shiropichu* improves circulation thereby correcting brain circulation which is very important for relieving headaches and also has a neuroprotective activity. It also enhances the function of special senses [43].

The overall effect of this formulation has been seen to reduce the symptoms seen in patients diagnosed with malignant brain tumors. The survival data suggest that the administration of RSS for a longer duration helps to build immunity and enhance the functioning of the brain leading to increase in survival period.

The current study focused solely on assessing the effects of oral Ayurvedic medications on glioblastoma patients, without incorporating panchakarma therapies due to patient eligibility constraints. Additionally, the dosage of RSS was tailored according to symptom severity and overall patient strength, rather than considering factors like tumor grade or molecular analysis reports. Notably, no adverse events were observed during the treatment period.

5. Conclusion

This retrospective cohort study sheds light on the promising effects of *Raupya Suvarna Sutashekhara* (RSS) in individuals with glioma. RSS, a unique blend of incinerated metals like silver, gold, mercury, copper, conch, and herbal extracts, was administered to glioblastoma patients. Among the 110 patients meeting the criteria, four groups were formed, receiving doses of 125 mg of RSS once or twice daily for durations ranging from 3 months to 5 years.

The results demonstrate the beneficial impact of RSS on glioma patients, reflected in improvements in clinical symptoms, weight, Karnofsky Performance Status (KPS), Quality of Life (QoL) scores, and survival outcomes. Longer treatment duration and higher disease grade were associated with improved patient survival. Symptoms related to memory, headache, balance, and digestion showed significant

improvement. However, there were no notable changes observed in symptoms like vision changes, facial numbness or tingling, swallowing difficulties, and tingling in extremities.

In summary, adjunct Ayurvedic treatment, particularly with RSS, appears to mitigate symptom severity and uphold the quality of life for patients with malignant brain tumors. Despite the aggressive nature of gliomas, treatment with RSS correlated with increased patient survival, particularly with longer durations of administration. This suggests that RSS holds promise in addressing both tumor-related symptoms and side effects of conventional treatments.

Further, to validate these findings, prospective randomized controlled trials or case-control studies in high and low-grade glioblastoma patients, incorporating RSS alongside *Panchakarma* modalities, can be considered. Such studies would provide deeper insights into the efficacy and potential mechanisms of action of RSS in glioma management.

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Author contributions

Author 1 – SS and Author 3 AK: Conception or design of the work, Drafting the work or revising it critically for important intellectual content, final approval of the version to be published, Agreement to be accountable for all aspects of the work.

Author 2-VD: Conception or design of the work, Acquisition of the work, analysis, interpretation, Drafting the work or revising it critically for important intellectual content, final approval of the version to be published, Agreement to be accountable for all aspects of the work.

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Declaration of competing interest

This formulation has been applied for Indian Patent and published under File No. 201721007554 as “Formulation for Management of Brain Tumors and Process of Preparation Thereof.

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