

# Complementary and alternative medicine in children with diffuse intrinsic pontine glioma—A SIOPE DIPG Network and Registry study

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## Abstract

**Introduction:** Diffuse intrinsic pontine glioma (DIPG) is a rare and aggressive childhood brainstem malignancy with a 2-year survival rate of <10%. This international survey study aims to evaluate the use of complementary and alternative medicine (CAM) in this patient population.

**Methods:** Parents and physicians of patients with DIPG were asked to participate in a retrospective online survey regarding CAM use during time of illness.

**Results:** Between January and May 2020, 120 parents and 75 physicians contributed to the online survey. Most physicians estimated that <50% of their patients used CAM, whereas 69% of the parents reported using CAM to treat their child during time of illness. Cannabis was the most frequently used form of CAM, followed by vitamins and minerals, melatonin, curcumin, and boswellic acid. CAM was mainly used with the intention of direct antitumor effect. Other motivations were to treat side effects of chemotherapy or to increase comfort of the child. Children diagnosed from 2016 onwards were more likely to use CAM ( $\chi^2 = 6.08$ ,  $p = .014$ ). No significant difference was found between CAM users and nonusers based on ethnicity ( $\chi^2 = 4.18$ ,  $p = .382$ ) or country of residence ( $\chi^2 = 9.37$ ,  $p = .154$ ). Almost 50% of the physicians do not frequently ask their patients about possible CAM use.

**Abbreviations:** CAM, complementary and alternative medicine; CNS, central nervous system; DIPG, diffuse intrinsic pontine glioma; GBM, glioblastoma; NCCIH, US National Center for Complementary and Integrative Health; ROS, reactive oxygen species; SIOPE BTG, International Society of Pediatric Oncology Europe Brain Tumor Group

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**Conclusion:** This survey demonstrates that worldwide, a considerable number of patients with DIPG use CAM. Physicians should be more aware of potential CAM use and actively discuss the topic. In addition, more research is needed to gain knowledge about possible anticancer effects of CAM and (positive/negative) interactions with conventional therapies.

**KEYWORDS**

boswellic acid, cannabis, complementary and alternative medicine (CAM), curcumin, diffuse intrinsic pontine glioma (DIPG)

## 1 | INTRODUCTION

Diffuse intrinsic pontine gliomas (DIPGs) comprise approximately 15–20% of central nervous system (CNS) tumors in children and have a poor prognosis.<sup>1</sup> With a median overall survival of 11 months and 2-year survival rates below 10%, they are the leading cause of brain tumor-related deaths in children.<sup>2–5</sup> Due to the delicate location of the tumor, surgical resection is not an option, and no effective chemotherapy regimens have been identified for DIPG thus far. To date, radiotherapy remains the only proven, although temporarily effective, therapy.<sup>6</sup>

With a high risk of death and only minimal efficacy of conventional therapies, patients tend to turn toward complementary and alternative treatment strategies.<sup>7</sup> The US National Center for Complementary and Integrative Health (NCCIH) defines complementary and alternative medicine (CAM) as “a group of diverse medical and healthcare interventions, practices, products, or disciplines that are not generally considered part of conventional medicine.”<sup>8</sup> The NCCIH divides CAM into two main groups: (i) natural products, such as botanicals, vitamins, and minerals, and probiotics; and (ii) mind and body practices, such as yoga, chiropractic manipulation, massage, and meditation.<sup>8</sup>

The extent and type of CAM used by patients with DIPG is largely unknown. More in general, the use of CAM by pediatric cancer patients has been well documented. A systematic review from 2010 including 20 articles that investigated CAM usage in pediatric cancer patients ( $n = 3166$ ) showed a prevalence ranging from 20% to 60%.<sup>9</sup> Natural products, such as herbal remedies and dietary and nutritional interventions, were the most commonly used forms of CAM based on these studies. However, the prevalence rates varied drastically from 2% to 48%, and no specific herbs or diets were described.<sup>9</sup> Moreover, patients in this systematic review encompassed a broad spectrum of diagnoses, but brain tumor patients were underrepresented, as only 14% had CNS tumors.

In adult glioma patients, Heese et al. surveyed CAM usage ( $n = 621$ ; mean age 44 years) and demonstrated that 40.3% used CAM.<sup>10</sup> Unfortunately, this study also did not mention the specific type of CAM used.<sup>10</sup> Furthermore, in 2014 a survey was conducted among US oncologists and hematologists ( $n = 392$ ) to investigate their knowledge and practices regarding CAM use. This study showed that 41% of these healthcare professionals discussed CAM usage with their patients, however, only when patients initiated such conversations.<sup>11</sup>

Considering these generalized analyses of CAM usage and the significant heterogeneity of patient populations, more focused studies are needed to understand the use of unconventional medicine in specific settings. Therefore, in the present study, we aim to determine if and what kind of CAM is used by patients with DIPG, along with supporting information such as motivation, frequency of use, and whether or not their use was discussed with a physician. Moreover, we aim to determine the knowledge and behavior of healthcare professionals treating patients with DIPG regarding their patients' CAM use. Together, these data will provide more insight into the status of CAM use in DIPG and enable more targeted studies in the future.

## 2 | METHODS

### 2.1 | Approval

This study was approved by the Medical Ethical Committee of the Amsterdam UMC - location VU University Medical Center (METc VUmc, study number: VUMC2019.503). The ethical committee declared that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study.

### 2.2 | Online survey

Two online surveys, one for parents and/or caregivers of patients with DIPG (Dutch and English version) and one for healthcare professionals treating patients with DIPG (English version), were developed based on previously published CAM questionnaires.<sup>12,13</sup> The questionnaires were published online via the online survey software Surveylyzer. Parents and/or caregivers of patients with DIPG were recruited anonymously via (i) parent foundations such as the Semmy Foundation (Netherlands) and the Cure Starts Now Foundation (United States), or (ii) via their treating physician in countries that do not have widely active parent foundations. Physicians and parent foundations were asked to distribute the link to the online questionnaire together with an explanatory fixed text among their patients or members (for example via their website, email, or newsletter). Healthcare professionals treating patients with DIPG were recruited via the electronic mailing list of

the International Society of Pediatric Oncology Europe Brain Tumor Group (SIOPE BTG). The surveys were available for a total period of 20 weeks, from January through May 2020. Reminders were sent 8 and 15 weeks after initial survey distribution.

Both surveys queried the use of CAM in patients with DIPG during time of illness. Participants were asked to describe if they ever used, or for physicians, prescribed CAM to treat patients with DIPG, including frequency of and motivation for usage. The complete surveys can be found in the Supporting Material.

### 2.3 | Statistics

Data obtained from the surveys were analyzed by descriptive statistical methods using IBM SPSS Statistics version 26. The Pearson's chi square test was used to determine whether there is a statistically significant difference between CAM users and nonusers ( $p < .05$ ).

## 3 | RESULTS

One hundred twenty parents and/or caregivers and 75 healthcare professionals treating patients with DIPG worldwide contributed to the online survey. As the survey was anonymously distributed via parent foundations, physicians and the electronic mailing list of the SIOPE BTG, also including professionals not (directly) involved in the treatment of patients with DIPG, it was not possible to determine the overall response rate for both surveys.

Parents and/or caregivers of patients with DIPG diagnosed between 2000 and 2020 participated in this survey. The median age of the child at diagnosis was 6.5 years (range 1–16 years). Table 1 contains demographic data of the responding parents and/or caregivers of patients with DIPG.

Sixty-nine percent of the parents and/or caregivers of patients with DIPG who responded to the survey treated their child with any form of CAM. When using CAM, almost all parents reported this to be complementary to conventional treatment (90.4%), and <10% reported CAM use as an alternative to conventional treatment. All parents reported to use CAM with the intention to actively treat the tumor and with the motivation to have tried everything to treat their child. Besides treating the tumor, CAM was also used to (i) treat side effects of chemotherapy (49.4%), (ii) support the immune system (6.1%), (iii) treat anxiety (3.6%), or (iv) limit the use of corticosteroids (3.6%). All parents and/or caregivers who used CAM to treat their child used natural products, and 47.5% of these parents also tried mind and body practices, such as massages, aromatherapy, spiritual healing (e.g., meditation, prayer, yoga), music therapy, magnetic therapy, and (biophoton or star-) light therapy. There is a significant difference in the use of CAM by parents and/or caregivers of children diagnosed before 2016 and after ( $\chi^2 = 6.08$ ,  $p$ -value = .014). More parents used CAM when their child was diagnosed in 2016 or later. The median age at diagnosis of children who used CAM was not different from children who did not use CAM; in both groups, the median age was 6.5 years. No significant differences were found between parents and/or caregivers who gave CAM to their

child versus those who did not, with respect to (i) ethnicity ( $\chi^2 = 4.18$ ,  $p$ -value = .382), (ii) country of residence ( $\chi^2 = 9.37$ ,  $p$ -value = .154), and (iii) educational level of the mother ( $\chi^2 = 3.88$ ,  $p$ -value = .423) or the father ( $\chi^2 = 1.40$ ,  $p$ -value = .845).

Among the healthcare professionals who responded to the survey, 84% were pediatric oncologists. Others were child neurologists, radiation oncologists, and pediatric neurosurgeons. Most of the respondents (70.7%) treat up to five patients with DIPG per year. Table 2 contains demographic data of the responding healthcare professionals.

Seventy-three percent of the healthcare professionals indicated that they never prescribe any form of CAM. A minority (9.3%) did prescribe CAM to patients with DIPG in order to actively treat the tumor. Others prescribed CAM to treat side effects of conventional therapies. No significant differences in ethnicity ( $\chi^2 = 3.05$ ,  $p$ -value = .995) or country of residence ( $\chi^2 = 12.54$ ,  $p$ -value = .638) were found between physicians prescribing CAM versus physicians who did not. Most healthcare professionals estimated that less than 50% of their patients with DIPG use CAM (Table 3). When using CAM, 53.3% of the healthcare professionals estimated that their patients use it on daily basis.

Figure 1 provides an overview of the type of CAM used by patients with DIPG, as mentioned by both parents and/or caregivers and healthcare professionals. The top five most frequently used CAM were (i) cannabis (CBD/THC), (ii) vitamins and minerals (vitamin A/B/C/D, zinc, iron, omega 3/6), (iii) melatonin, (iv) curcumin, and (v) boswellic acid and other dietary supplements. Other natural products parents mentioned to have used to treat their child were ezcozul (scorpion poison;  $n = 2$ ), graviolia fruits ( $n = 3$ ), essential oils ( $n = 5$ ), various plants and algae ( $n = 5$ ), and various diets and teas ( $n = 5$ ). When using CAM, 60% of the parents and/or caregivers gave CAM to their child on a daily basis. Most parents and/or caregivers bought their CAM products via unlicensed resellers or partners, for example online (31.3%) or via a third party that manufactured CAM especially for their child (13.3%; Table 4).

Thirty-two percent of the parents and/or caregivers did not feel they could freely discuss CAM usage with their child's physician. They were afraid of (i) disapproval and rejection by their child's physician (21.7%), (ii) the risk of doctors stopping their conventional treatment or excluding them from participating in a clinical trial (5.8%), or (iii) the risk of involvement of child services as some CAMs, such as cannabis, are considered illegal in several countries (4.2%). Among the physicians, 46.7% reported to not frequently ask their patients about possible CAM usage. The same physicians also reported to expect that, if not actively asked by them, patients would not discuss possible CAM usage with them.

## 4 | DISCUSSION

With this international survey study on the use of CAM in patients with DIPG, we demonstrated that up to 70% of the parents and/or caregiver of patients with DIPG use CAM to treat or comfort their child during time of illness. This is a higher percentage than estimated by most healthcare professionals, whom predicted that less than 50% of their patients with DIPG use CAM.

**TABLE 1** Demographic data of participating parents and/or caregivers of patients with diffuse intrinsic pontine glioma (DIPG)

|                                                         | <i>n</i> = 120 | %      |
|---------------------------------------------------------|----------------|--------|
| <b>Gender of child</b>                                  |                |        |
| Male                                                    | 57             | 47.5   |
| Female                                                  | 63             | 52.5   |
| <b>Child's age at diagnosis (years), median [range]</b> | 6.5            | [1–16] |
| <b>Year of diagnosis</b>                                |                |        |
| ≤2015                                                   | 23             | 19.2   |
| ≥2016                                                   | 97             | 80.8   |
| <b>Ethnicity</b>                                        |                |        |
| Caucasian                                               | 99             | 82.5   |
| Hispanic                                                | 10             | 8.3    |
| Asian                                                   | 4              | 3.3    |
| Middle Eastern                                          | 2              | 1.7    |
| Multiracial                                             | 5              | 4.1    |
| <b>Highest education: Mother</b>                        |                |        |
| Primary school                                          | 1              | 0.8    |
| High school                                             | 53             | 44.2   |
| Bachelor degree                                         | 30             | 25.0   |
| Master's degree                                         | 36             | 30.0   |
| <b>Highest education: Father</b>                        |                |        |
| Primary school                                          | 3              | 2.5    |
| High school                                             | 44             | 36.7   |
| Bachelor degree                                         | 44             | 36.7   |
| Master's degree                                         | 29             | 24.2   |
| <b>Region</b>                                           |                |        |
| Northern Europe                                         | 2              | 1.7    |
| Western Europe                                          | 55             | 45.8   |
| Eastern Europe                                          | 11             | 9.2    |
| Northern America                                        | 42             | 35.0   |
| Mid/Southern America                                    | 6              | 5.0    |
| Australia                                               | 3              | 2.5    |
| India                                                   | 1              | 0.8    |

In several pediatric studies, rates of CAM use among pediatric cancer patients in general varied between 20% and 60%.<sup>9,14</sup> However, these studies were not restricted to pediatric glioma patients, and included several types of pediatric tumors, which limits comparability with our current study. When comparing our results to studies done in adult glioma patients, where prevalence rates vary between 40% and 50%, CAM usage rates prove to be higher in patients with DIPG.<sup>10,15</sup> In a survey focusing specifically on adults diagnosed with glioblastoma (GBM), 74% of the participants reported CAM use during time of illness.<sup>16</sup> This is more in line with the results of our study, and suggests that higher use of CAM could be related to poor prognosis, with tendency to seek alternative options besides conventional treatments. Nevertheless, no significant relationship between CAM use and grade of malignancy has been reported in previous studies.<sup>10,15,17,18</sup> Factors

that could possibly influence the high variability between the different studies could be related to inconsistent definitions of CAM and the lack of standardized and validated tools to assess CAM usage in the cancer population.

Our study shows significant differences in CAM use by parents and/or caregivers of patients with DIPG diagnosed before and after 2016. This could be partly explained by the increased availability of information regarding CAM; over the years, more information regarding diseases and possible treatments can be found on the internet and people are becoming more skilled in finding such information. Moreover, there is an increasing number of internet forums for parents of children suffering from DIPG, where parents connect and may exchange information regarding alternative ways to support their child. These parent communities/forums may form one of the limitations of

**TABLE 2** Demographic data of participating healthcare professionals treating patients with diffuse intrinsic pontine glioma (DIPG)

|                                                 | <i>n</i> = 75 | (%)     |
|-------------------------------------------------|---------------|---------|
| <b>Gender</b>                                   |               |         |
| Male                                            | 34            | 45.3    |
| Female                                          | 41            | 54.7    |
| <b>Age (years), median [range]</b>              | 49            | [35–66] |
| <b>Ethnicity</b>                                |               |         |
| Caucasian                                       | 67            | 89.3    |
| Hispanic                                        | 2             | 2.7     |
| Asian                                           | 2             | 2.7     |
| Middle Eastern                                  | 1             | 1.3     |
| Multiracial                                     | 3             | 4.0     |
| <b>Medical specialty</b>                        |               |         |
| Pediatric oncologist                            | 63            | 84.0    |
| Child neurologist                               | 1             | 1.3     |
| Radiation oncologist                            | 5             | 6.7     |
| Pediatric neurosurgeon                          | 3             | 4.0     |
| Other                                           | 3             | 4.0     |
| <b>Number of DIPG patients treated per year</b> |               |         |
| <5                                              | 53            | 70.7    |
| 5–10                                            | 19            | 25.3    |
| >10                                             | 3             | 4.0     |
| <b>Region</b>                                   |               |         |
| Northern Europe                                 | 8             | 10.7    |
| Western Europe                                  | 42            | 56.0    |
| Eastern Europe                                  | 8             | 10.7    |
| Southern Europe                                 | 15            | 20.0    |
| Northern America                                | 1             | 1.3     |
| Hong Kong                                       | 1             | 1.3     |

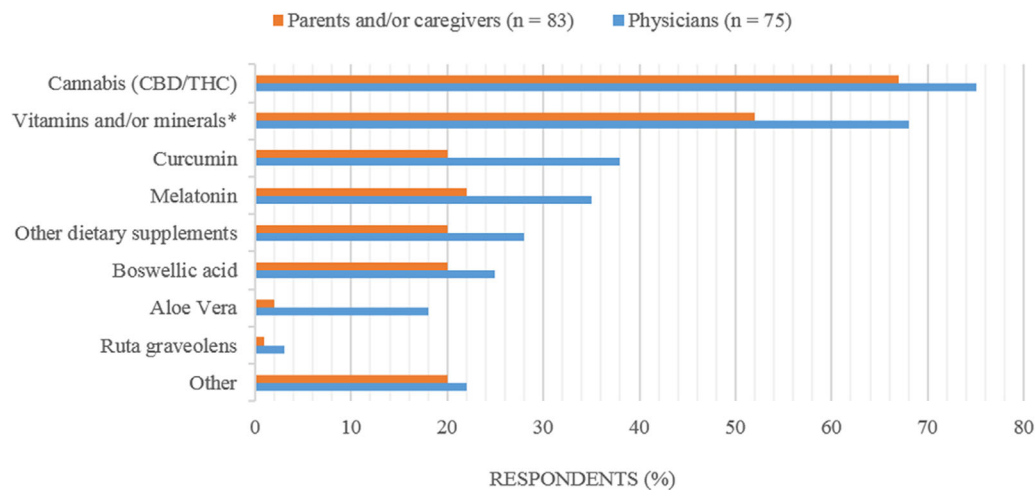
**TABLE 3** Physicians' estimated percentage of complementary and alternative medicine (CAM) use among their patients with diffuse intrinsic pontine glioma (DIPG)

|        | <i>n</i> = 75 | %    |
|--------|---------------|------|
| <25%   | 33            | 44.0 |
| 25–50% | 13            | 17.3 |
| 50–75% | 20            | 26.7 |
| >75%   | 9             | 12.0 |

this study, since these communities/forums were used to distribute this survey, there could be a form of selection bias in the sense that more online-active parents may have participated who might also be the ones who use more CAM. Moreover, the number of parents and/or caregivers of children diagnosed in 2016 and onwards that participated in our study is significantly higher than the number of parents and/or caregivers of patients with DIPG diagnosed before 2016. To have an unbiased overview of the actual incidence of CAM use among patients with DIPG for future purposes, this information needs to be gained

prospectively by actively asking patients about CAM use. This could be integrated in the registration process of patients in the European and International DIPG Registries.<sup>19</sup>

An interesting result of our analysis is the fact that no significant differences in ethnicity and country of residence were found between parents and/or caregivers who gave their child CAM versus those who did not. A possible explanation for this might be that our study population does not encompass all ethnicities equally and that not all countries are well represented. Especially, the



**FIGURE 1** Types of complementary and alternative medicines (CAMs) used by patients with diffuse intrinsic pontine glioma (DIPG) based on responses of their parents and/or caregivers and their physicians (\*vitamin A/B/C/D, zinc, iron, omega 3/6)

**TABLE 4** Sources where parents and/or caregivers of patients with diffuse intrinsic pontine glioma (DIPG) buy complementary and alternative medicine (CAM)

|                                              | n = 83    | %           |
|----------------------------------------------|-----------|-------------|
| <b>Licensed</b>                              | <b>31</b> | <b>37.3</b> |
| Pharmacy                                     | 22        | 26.5        |
| Drug/herbal store                            | 9         | 10.8        |
| <b>Unlicensed</b>                            | <b>45</b> | <b>54.2</b> |
| Online                                       | 26        | 31.3        |
| Third party                                  | 11        | 13.3        |
| Black market                                 | 8         | 9.6         |
| <b>Combination of above-mentioned places</b> | <b>7</b>  | <b>8.4</b>  |

non-Western countries are underrepresented in our study population, which could mean that 69% is an underestimation of the actual use of CAM among patients with DIPG, as there is evidence suggesting that cultural differences are the main driver behind the difference in CAM use worldwide. In Asian, Middle-Eastern, Sub-Saharan African, or Latin American countries, CAM use is deeply rooted in their ancient traditional medicinal practices, and thus more commonly used.<sup>20-23</sup>

In our survey, parents and/or caregivers indicated that the main motivation to use CAM was to actually treat the tumor. One of the most frequently used forms of CAM for this purpose was cannabis. It is hypothesized that the potential anticancer effects of cannabinoids involve inhibition of proliferation, autophagy induction, anti-angiogenesis, inhibition of endothelial-to-mesenchymal transition, and inhibition of inflammation.<sup>24,25</sup> Other CAMs frequently used for this purpose were vitamins, such as vitamin C because of the supposed anticancer effects via antioxidation and creation of free radicals (reactive oxygen species [ROS]),<sup>26,27</sup> and vitamin D that has been described to have cytotoxic effects in patients and cell lines, including GBM. The full mechanism of action of these substances, however, remains

unknown.<sup>28-31</sup> Moreover, there are contradicting reports regarding the possible anticancer effects of zinc and iron supplements. Both minerals form complexes that could render an anticancer effect, although the same complexes may also protect the tumor cells from radiation and stimulate cell proliferation.<sup>32,33</sup> This is similar for omega-3 and -6 fatty acids, with limited evidence supporting an anticancer effect and some data suggesting a positive effect on tumor cells.<sup>34-36</sup> Also, melatonin, a potent antioxidant with possible anticancer effects in studies using glioma cells, is used for its potential anticancer effects. Several preclinical studies on glioma cells suggest a role for melatonin in (i) reducing cell proliferation,<sup>37,38</sup> (ii) inducing apoptosis,<sup>39</sup> (iii) inhibiting cell migration and formation of metastasis,<sup>40</sup> (iv) inhibiting autophagy, and (v) inhibiting cell self-renewal.<sup>38,41</sup> The same holds true for curcumin, which has been preclinically investigated for its role in GBM, ultimately concluding that curcumin is a potentially effective anticancer option for GBM.<sup>42</sup> All studies documented a reduction in GBM cell viability through various molecular pathways, and animal studies suggested improved survival with curcumin compared to placebo.<sup>43-45</sup> However, there are no clinical data available to truly support any of these preclinical results yet.



Another frequently used CAM, boswellic acid, is not primarily used for its potential anticancer effect but mainly for its anti-inflammatory effects possibly based on inhibition of prostaglandin E synthase-1 enzyme.<sup>46</sup> Boswellic acid significantly reduces edema in brain cancer patients, similar to dexamethasone, but with less side effects.<sup>47</sup> Although not investigated in a comparative trial with steroids, it is possible that boswellic acid could potentially allow for steroid sparing.<sup>47</sup>

Apart from whether or not CAM could have an anticancer effect, combining apparently innocent CAM with conventional treatment could result in unintended drug interactions. For example, there is a controversy surrounding concomitant use of antioxidants, such as vitamin C and melatonin, and ROS-dependent chemotherapeutics such as cisplatin, doxorubicin, and arsenic agents. It is possible that antioxidants neutralize the ROS required for the chemotherapeutic cytotoxicity of these chemotherapeutics.<sup>48,49</sup> Another example is the possible inactivation of platinum derivatives, such as carboplatin and cisplatin by omega-3 fatty acids, resulting in ineffective treatment.<sup>50</sup> Moreover, cannabis and melatonin are also known inhibitors of several cytochrome P450 (CYP) enzymes, which could lead to higher plasma concentrations of concomitantly administered chemotherapeutic agents that are substrates for these enzymes.<sup>51,52</sup>

Because CAMs could possibly have either beneficial or harmful effects, it is important for physicians to prospectively monitor CAM use by patients with DIPG and freely discuss this topic with their parents. Overall, most healthcare professionals seem to have a negative attitude toward CAM, and they tend to discourage its use. Many parents and/or caregivers, however, are more willing to use CAM in order to have tried everything possible to treat their child. Not being able to discuss this with the child's treating physician could create disharmony in the relationship between parents and physician. By prospectively monitoring CAM use, more information regarding the used formulations, dosages, and treatment schedules could be obtained. Additionally, monitoring CAM use could also lead to more knowledge regarding its effects on conventional treatments, such as potential negative interactions or beneficial synergistic effects.

Our study demonstrates that a substantial number of patients with DIPG worldwide use CAM and that this is not often discussed with the treating physician. To date, there have been limited clinical studies assessing the impact of CAM, and its effects could range from beneficial to harmful. Either way, CAM has become a part of pediatric healthcare that can no longer be ignored. Physicians play an important role in preventing or encouraging CAM use. Therefore, more research is needed to obtain deeper knowledge about the possible anticancer effects of CAM and their effects on conventional therapies, if any. By acquiring this information and openly discussing the topic, physicians can inform their patients more completely, creating a more holistic treatment paradigm and strengthening the patient-physician relationship.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest relevant to this article.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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