



SUPPLEMENT ARTICLE

Nutritional traditional and complementary medicine strategies in pediatric cancer: A narrative review

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Abstract

Traditional and complementary medicine (T&CM) strategies are commonly used by pediatric cancer patients. Nutritional approaches to T&CM include bioactive compounds, supplements, and herbs as well as dietary approaches. Pediatric cancer patients and their families commonly request and use nutritional T&CM strategies. We review the potential risks and benefits of nutritional T&CM use in pediatric cancer care and provide an overview of some commonly used and requested supplements, including probiotics, antioxidants, cannabinoids, vitamins, turmeric, mistletoe, *Carica papaya*, and others. We also discuss the role of specific diets such as the ketogenic diet, caloric restriction diets, whole-food diets, and immune modulating diets. There is a growing body of evidence to support the use of some T&CM agents for the supportive care of children with cancer. However, further study is needed into these agents and approaches. Open communication with families about T&CM use is critical.

KEYWORDS

nutrition, pediatric oncology, supportive care, traditional and complementary medicine

1 | INTRODUCTION

Traditional and complementary medicine (T&CM) strategies include medicines and practices to support health that are outside of the conventional medicine paradigm. As defined by the National Center for Complementary and Integrative Health (NCCIH), T&CM practices can include biologically based therapies such as herbs and supplements, mind-body interventions, such as yoga or tai chi, and alternative medical systems such as Traditional Chinese Medicine.¹ Both self-directed and practitioner-led T&CM are commonly used by children with cancer and their families worldwide.² Despite a lack of empiric evidence for their effectiveness in curing malignancy, many families are utilizing T&CM strategies with curative intent.³ Many families and patients also use T&CM strategies to address supportive care-related issues including chemotherapy-induced nausea and vomiting, anxiety, and risk of

infection.⁴ Yet, < 50% of families disclose using T&CM agents to their child's oncology team, and some families even abandon conventional cancer care to pursue T&CM therapies in isolation.^{2,5-7} As such, it is imperative that pediatric oncology health providers have open discussions with their patients and families about T&CM agents, and have an understanding of the potential risks and benefits of T&CM use in cancer care to facilitate open and inclusive discussion. Open and inclusive discussion has the potential to allow for safe integration of T&CM strategies into conventional care, and for increased knowledge sharing between patients and providers. This narrative review will focus on commonly used nutritional T&CM strategies, their potential risks and benefits, and provide an overview of current evidence. A summary of definitions is provided in Table 1.

2 | POTENTIAL RISKS AND BENEFITS OF T&CM

There are unique risks associated with the use of T&CM therapies. One of the largest risks is as a result of the less stringent regulation

Abbreviation: ALL, acute lymphoblastic leukemia; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CBD, cannabidiol; COG, Children's Oncology Group; FDA, Food and Drug Administration; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; NCCIH, National Center for Complementary and Integrative Health; T&CM, traditional and complementary medicine; THC, tetrahydrocannabinol.

TABLE 1 Definitions of nutrition-related traditional and complementary medicine (T&CM) strategies

Term	Definition
Functional food (or bioactive food)	Whole foods with potential health benefits beyond basic nutrition, often promoting health and reducing the risk of disease. ¹⁰⁶
Bioactive compound	A substance typically found in functional foods, such as probiotics, fiber, or minerals, thought to be responsible for changes in health status. ¹⁰⁷
Supplement	A nonfood substance or combination of substances, including vitamins, minerals, herbs, plant-based products, or other bioactive compounds taken with the intent of improving health. ¹⁰⁸
Nutraceuticals	Foods that include both functional foods and foods that have been supplemented with additional bioactive compounds for the purposes of improving health. ¹⁰⁹
Immunonutrition	Use of specific nutritional supplements or foods to modulate the immune system. ¹⁰⁴

of T&CM agents as compared with prescription drugs. In many countries, dietary T&CM products are classified as dietary supplements and thus they are exempt from drug regulations through agencies such as the Food and Drug Administration (FDA) in the United States or Health Canada in Canada.⁸ There is wide variability in the quality of available products, and products may be mislabeled⁹ or contaminated with heavy metals, microbial organisms, or other pharmaceutical agents.^{10,11} Although the FDA and Health Canada are working to provide additional oversight, patients should be aware that T&CM products are regulated differently from medications.

In patients with cancer undergoing chemotherapy, there are concerns about the potential for interactions with the use of dietary supplements, which may increase toxicity or decrease the effectiveness of chemotherapy.¹²⁻¹⁴ The efficacy of methotrexate (MTX) is known to be directly affected by folic acid; however, dietary studies in pediatric acute lymphoblastic leukemia (ALL) suggest that intake of folate through diet and fortification does not have an adverse effect on MTX activity, unless the doses of folate given are very high.¹⁵ Most interactions between bioactive compounds and chemotherapies in children have not been specifically investigated, and thus patients and families should be cautioned about this risk. Oncologists and oncology pharmacists can often provide some insight where there are known interactions by cross-referencing the chemotherapy agents in a child's treatment plan with the T&CM agents a family is hoping to use.¹⁶

A less overt risk of the use of T&CM strategies is their cost.¹⁷ Having a child diagnosed with cancer and undergoing treatment comes with a significant financial burden for families, even when controlled for insurance status.¹⁸ Many dietary supplements are costly, and often not covered by insurance. Costs of T&CM may vary significantly based on product used, amount, services engaged, and on location. In families who are already facing a significant financial burden, the additional cost of therapies of uncertain or unproven benefit may represent a significant risk.^{8,17}

Nutritional status is of essential importance to children with cancer. Children who are malnourished have inferior tolerance of side effects, increased risk of infection, lower quality of life, and decreased survival.^{19,20} Many children are already malnourished at presentation with cancer, both in high-income and low- and middle-income countries.²¹ If dietary T&CM strategies are used to the exclusion of a more balanced diet, it may put the child at risk for further malnourishment. Although the use of exclusionary diets is unusual, providers should be aware of their associated risks.

Although there are potential risks associated with T&CM strategies, they are being widely used across the globe.² Many T&CM strategies have important cultural significance, particularly among indigenous peoples for whom traditional medicine is central to their approach to health and wellness.²² Incorporation of these strategies into conventional pediatric oncology treatment may provide more holistic care to these families. For many oncologists, the uncertainty and risks associated with T&CM lead to a reluctance to engage in conversations about T&CM with families, providing instead only dissuasion toward all T&CM practices. Based on the clinical experience of the authors, having open and honest discussions about the risks and benefits of individual practices is optimal, and can lead to minimizing abandonment of conventional cancer therapy to pursue T&CM exclusively. There are no identified cases whereby exclusive use of T&CM has been curative for a child with cancer.^{23,24} It is therefore imperative that oncologists work to harmonize T&CM with conventional care where families desire.

3 | NATURAL HEALTH PRODUCTS

There are many nutritional compounds that have been suggested to have anticancer benefits.^{25,26} Providing a comprehensive guide of every agent in use is outside of the scope of this review. We provide an overview of agents that are commonly sought based on the clinical experience of the authors. See Table 1 for definitions of the some of the most commonly used terms throughout this review.

In a recent systematic review of T&CM agents used for curative intent, there were no high-quality studies in pediatric oncology demonstrating the effectiveness of T&CM agents in achieving pediatric cancer cures.³ A similar systematic review of T&CM agents used for supportive care in pediatric oncology summarized evidence for the use of bioactive compounds for supportive care indications.⁴

3.1 | Prebiotics and probiotics

Prebiotics are compounds that induce the growth or activity of beneficial intestinal microflora.²⁷ A single prospective randomized controlled trial of a prebiotic enriched formula was conducted in children undergoing chemotherapy. The formula was well tolerated, and patients who received the formula had a modest increase in levels of beneficial bacteria in the intestine.²⁸ The potential clinical benefit of prebiotics in children with cancer remains unclear and further study is required.²⁷

Probiotics are live microorganisms consumed to supplement or restore beneficial bacteria that help maintain that natural

intestinal microflora.²⁷ Preclinical models suggest that probiotics may ameliorate the risk of infection associated with graft-versus-host disease^{29,30} and play an important role in healthy weight management in children.³¹ Recent studies have investigated the safety and efficacy of probiotics in the pediatric oncology population. A placebo-controlled study conducted in Japan demonstrated reduced frequency and duration of febrile episodes in children treated with *Bifidobacterium breve*; there was no increased risk of invasive infection associated with administration of probiotics in this study.³² A recent pilot study demonstrated the safety and feasibility of using *Lactobacillus plantarum* in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) with severe neutropenia.³³ Of note, probiotic agents obtained for this study were certified free of bacterial and fungal contamination. Risk of infection associated with probiotic consumption may be related to strain or contamination of products.^{10,34} A Children's Oncology Group (COG) randomized controlled trial of the effectiveness of *Lactobacillus plantarum* in preventing graft-versus-host disease in children undergoing HSCT is currently undergoing enrollment (NCT03057054). The clinical benefit, appropriate strain, dose, and optimal administration of probiotics remain to be determined.

3.2 | Antioxidants

Antioxidants prevent oxidation, theoretically protecting the body against oxygen-free radicals and cell damage.³⁵ In the setting of cancer therapy, radiation and some chemotherapies are associated with the creation of oxygen-free radicals, which can contribute to both their anticancer and toxic side effects.³⁵ Antioxidants are found naturally in foods and can include vitamins C and E (discussed below), some minerals, such as selenium, and flavonoids found in fruit, wine, and soy.^{36,37} However, supplementation with antioxidant supplements in the setting of cancer has demonstrated mixed results; some studies show that antioxidants can antagonize the cytotoxic effects of chemotherapy and particularly radiotherapy, reducing their effectiveness,^{38,39} whereas others demonstrate that chemotherapy is less effective in the setting of oxidative stress,⁴⁰ and that appropriate levels of antioxidants are associated with fewer therapy delays and less chemotherapy toxicity.^{41,42} The impact of antioxidant therapy may also depend on the timing of the administration. Given these data, high-dose antioxidant supplementation that exceeds the upper limits as defined by the dietary reference intakes should be discouraged.³⁹

3.3 | Cannabinoids

There has been extraordinary public interest in the use of cannabis and cannabinoids for the treatment of pediatric cancer and cancer-related side effects. Cannabinoids include tetrahydrocannabinol (THC), which is the primary psychoactive compound in cannabis, and cannabidiol (CBD). Recently, particular attention has been paid to CBD oil as a cancer "cure." Clinically available cannabinoids include nabilone and dronabinol.⁴³

Despite the public enthusiasm for the efficacy of cannabinoids in treating cancer, evidence is lacking. Preclinical studies have shown some potential antitumor properties of cannabis and cannabinoids.⁴⁴ There are only limited clinical adult studies and no interventional studies at all in children demonstrating efficacy.⁴³ A prospective observational cohort study of medical marijuana in pediatric brain tumor patients is currently investigating this issue (NCT03052738). However, medical marijuana use has been implicated in serious clinical effects in children with cancer, such as hypotension.⁴⁵ Further study is required before these agents can be recommended. For an overview of issues related to cannabis and cannabinoid use in pediatric oncology, see the review by Ananth and colleagues.⁴³

Cannabinoids have demonstrated efficacy in the treatment of chemotherapy-induced nausea and vomiting in adults and in appetite stimulation in adults.^{46,47} Although synthetic cannabinoids such as nabilone and dronabinol are used for these indications in pediatric patients, their safety and efficacy have not been demonstrated in pediatric trials. Furthermore, the long-term impacts of these agents have not yet been studied. The American Academy of Pediatrics and Canadian Pediatric Society have issued position statements against the use of recreational cannabis and cannabinoid by youth because of concerns about brain development. Parents should be cautioned that the purity of other cannabinoids cannot be guaranteed and should not be used as a substitute for nabilone or dronabinol.

3.4 | Vitamins and supplements

Interest in the use of vitamins for the treatment of cancer has been long standing. In the 1970s, vitamin C was identified as a possible treatment for cancer and was investigated by prominent scientists, including the Nobel Prize winner Linus Pauling.⁴⁸ Since then, vitamin C has been investigated in multiple trials for a cancer treatment, without conclusive benefit being demonstrated.^{49,50} Vitamin C supplementation has not been specifically studied in pediatric cancers.

Vitamin D is purported to have anti-inflammatory and immunomodulatory effects and has thus garnered great interest as a potentially preventative or curative agent for cancers, based on epidemiologic studies that have shown a relationship between vitamin D deficiency and cancer risk.^{51,52} Vitamin D has an essential role in bone growth and health, particularly in the long term.⁵³ Vitamin D deficiency has been shown to be associated with oral mucositis during high-dose MTX treatment for children with ALL.⁵⁴ Low serum levels of vitamin D have also been associated with an inferior survival in European children with leukemia.⁵⁵ In North America, the vast majority of pediatric patients with ALL have been shown to have a deficit in vitamin D levels at diagnosis and throughout therapy.^{56,57} Recently, a study of Hodgkin lymphoma that included adolescents demonstrated that vitamin D deficiency was associated with impaired progression-free survival and impaired overall survival.⁵⁸ Given this constellation of findings, it is important to ensure children with cancer have sufficient vitamin D intake. The contribution of high-dose vitamin D supplementation is not yet known.

Several agents have been investigated for their effects on mucositis prevention. Glutamine, an amino acid, has been the most widely studied agent with studies showing conflicting results.⁵⁹⁻⁶² Vitamin supplementation for the prevention and treatment of mucositis has also been studied. A randomized trial comparing topical to systemic vitamin E showed a significant improvement in the treatment of mucositis in patients who received topical but not systemic vitamin E.⁶³ A subsequent randomized controlled trial of topical application of vitamin E or Pycnogenol (Maritime Pine) versus glycerin placebo showed benefit of both vitamin E and Pycnogenol in the treatment of grades 1-3 mucositis.⁶⁴ However, vitamin E has been shown to be ineffective in the prevention of mucositis.⁶⁵ Vitamin A was also evaluated for the prevention of mucositis and was found ineffective.⁶⁶ Traumeel S is a homeopathic remedy purported to have anti-inflammatory properties. It was evaluated in a COG phase 3 randomized placebo-controlled trial as a prevention and treatment for mucositis in patients undergoing HSCT, without demonstrated benefit.⁶⁷ Another trial demonstrated topical application of honey was helpful in mucositis in children with ALL.⁶⁸ At this juncture, there is no strong evidence for any supplementation that is of clear benefit in the setting of mucositis; however, topical vitamin E or honey may be helpful for some children.

Chemotherapy-induced febrile neutropenia is a common side effect associated with pediatric cancer treatment. In a population of South African children with cancer at risk of vitamin A deficiency, those with low levels of vitamin A (< 20 µg/dL) at diagnosis were shown to have a higher incidence of episodes of febrile neutropenia.⁶⁹ Although limited, these data may support appropriate vitamin A supplementation in children who are deficient. Further study of the prevalence of vitamin A deficiency and the safety of vitamin A supplementation is required. An open-label, matched pair study of fermented wheat germ extract conducted in 22 pediatric oncology patients showed fewer episodes of febrile neutropenia in children treated with the fermented wheat germ extract.⁷⁰ Further study is required of this agent to evaluate its potential efficacy and safety. A recent meta-analysis of studies of the use of topical honey for mucositis demonstrated benefit.⁷¹ In a randomized cross-over study from Egypt, raw, unprocessed clover honey was given to children with standard risk ALL in maintenance therapy.⁷² Honey twice weekly was shown to significantly decrease the number of admissions to the hospital for febrile neutropenia and the duration of those hospital admissions. Although these children did not experience adverse events, raw honey can contain spores of clostridium botulinum, which may confer a significant risk to immunocompromised children with cancer and infants less than one year of age; caution should be used.

There has been interest in the use of T&CM strategies for the prevention and treatment of MTX-induced hepatotoxicity. Omega 3 fatty acids, typically found in fish and some seeds, reduced liver enzymes and increased antioxidants in children with ALL undergoing maintenance therapy.⁷³ A multicenter pilot study of milk thistle demonstrated a decrease in aspartate aminotransferase (AST) and total bilirubin levels,⁷⁴ whereas another study showed that black seed oil decreased liver enzymes, alkaline phosphatase (ALP), and prothrombin time.⁷⁵ The risks and benefits of using any of these agents would require con-

sideration of the other medications in use, and the clinical situation of any child experiencing MTX-induced hepatotoxicity. Levocarnitine is a "vitamin-like" compound synthesized from lysine and plays an important role in the oxidation of fatty acids.⁷⁶ Levocarnitine has been studied as a potential treatment for asparaginase-induced hepatotoxicity, with case series demonstrating benefit.^{77,78} Further study into the safety and efficacy of this agent is needed before its use can be recommended.

Glutamic acid, a nonessential amino acid found in protein-rich foods, has been investigated in two studies of neurotoxicity. Although a pilot study showed improvements in paresthesias, constipation, and reflexes,⁷⁹ a larger multicenter consortium study did not find any benefit.⁸⁰ Glutamine has also been investigated as a potential intervention for vincristine-induced neuropathy. A recent pilot randomized controlled trial of glutamine for vincristine-induced neuropathy showed a clinically and statistically significant reduction in sensory neuropathy and an improvement in quality of life in children receiving glutamine.⁸¹

The endogenously produced sleep hormone melatonin is a commonly used supplement for sleep,⁸² with a growing interest in examining its antioxidant properties and its potential use as an appetite stimulant. There is evidence of benefit for use of melatonin for sleep in healthy children but no direct evidence in children with cancer.^{83,84} In a double-blind placebo-controlled trial of melatonin as an appetite stimulant in adults with advanced cancer, there was no benefit of melatonin over placebo.⁸⁵ There is a phase I trial being conducted for dose findings for melatonin for use as an appetite stimulant in children.⁸⁶ A variety of studies have examined the use of melatonin as an adjuvant to chemotherapy and radiation in adult patients with cancer, with a possible benefit of melatonin.⁸⁷ At present, there are no randomized controlled trials examining melatonin as a curative agent for pediatric cancers. Despite this lack of direct data, melatonin has recently been recommended by Children with Cancer (UK) as a standard of care to improve cure for all children with pediatric cancer in the United Kingdom; several pediatric oncologists have expressed concern.⁸⁸ At this juncture, there are inadequate data to recommend the use of melatonin as an antioxidant, as an appetite stimulant or for curative intent. Melatonin for sleep may be considered.

Selenium, an essential dietary trace mineral, has been examined in two different randomized, double-blinded cross-over trials among children with leukemia, lymphoma, and solid tumors. The first study demonstrated some improvements in fatigue and nausea by patient or proxy report, as well as renal and kidney function among those supplemented with selenium, whereas the second demonstrated improved neutrophil counts.^{89,90} A well-rounded diet should provide adequate selenium intake.

3.5 | Plant-based bioactive compounds and nutraceuticals

Turmeric is a rhizome plant, whose root is used as a spice in dishes from across the globe. Its most investigated active agent, curcumin, is purported to have immunomodulatory, anti-inflammatory,

chemopreventative, chemosensitizing, and radiosensitizing effects.⁹¹ Curcumin has been evaluated in adult patients with pancreatic cancer, with some antitumor activity being demonstrated.⁹² There are no published clinical studies of curcumin in pediatric cancer patients. Bioavailability of curcumin in humans appears to be poor⁹³; however, strategies to improve the bioavailability of curcumin are being investigated.⁹⁴ Topical turmeric has been studied in adults as an intervention for chemotherapy- and radiotherapy-induced mucositis with potential benefit demonstrated.^{95,96} No studies in children have been conducted to date. As curcumin is known to interfere with the P450 enzyme, it may impact on the metabolism of cyclophosphamide and doxorubicin, among other agents.⁹⁷ The risk of interaction is likely low because of the low gut absorption of curcumin. Although routine use of turmeric in food is likely safe, caution should be used when considering supplementation.

Mistletoe is a plant that grows on other trees and has been used in tea form for centuries to treat a variety of conditions. There are currently several oral, intravenous, and homeopathic formulations available, although safety and efficacy profiles differ between formulation and provenance.^{98,99} Among adults with cancer, there have been several studies investigating intravenous or subcutaneous European mistletoe use for both supportive care and curative intent.^{100,101} Two case reports of mistletoe therapy among children with lymphoid papulosis and cutaneous lymphoma have demonstrated resolution of the malignant cutaneous lesions with mistletoe monotherapy.^{102,103} As all patients in the reported clinical studies appear to have been adults, studies are necessary to determine the potential efficacy of mistletoe in children.

Carica papaya is a tropical plant whose fruits, leaves, and seeds have been widely used by indigenous peoples for supportive management of several diseases. In one preclinical study, *Carica papaya* leaf extract was shown to significantly inhibit proliferation of tumor cell lines.¹⁰⁴ These results have not yet been recapitulated in the clinical setting. The use of *Carica papaya* leaf extract for thrombocytopenia is gaining popularity in settings where platelet transfusion is not readily available. *Carica papaya* leaf extracts has been studied in the management of Dengue hemorrhagic fever where its use has been associated with increased platelet counts and shorter duration of hospitalization both for adult patients¹⁰⁵⁻¹⁰⁷ and pediatric patients.¹⁰⁸

4 | DIETS

Dietary strategies to manage illness have gained enormous popularity in the pediatric cancer population and in society at large.²⁶ The importance of nutrition in pediatric patients with cancer has been demonstrated in several well-designed clinical studies. Dietary strategies may help promote health; however, overly restrictive diets may deprive children of essential nutrients and may contradict accepted clinical practice guidelines for pediatric cancer care.^{20,109,110} Engaging a dietitian in the management of these patients is critical to ensure optimal nutritional status throughout the course of therapy.

4.1 | Ketogenic diet

The ketogenic diet is a high-fat, low-protein, and very low carbohydrate diet that has recently garnered significant public interest. Patients with intractable epilepsy have been successfully treated with the ketogenic diet.¹¹¹ The rationale for the use of the ketogenic diet in oncology patients is based on the Warburg observation that cancer cells rely on glucose for metabolism.¹¹² However, evidence of benefit from the ketogenic diet in cancer is lacking.¹¹³ There are no high-quality studies of the use of the ketogenic diet in pediatric cancer patients. Case series have demonstrated their use in pediatric patients with gliomas, with conclusions on the effectiveness unclear.¹¹⁴ A phase II trial of the ketogenic diet in patients with relapsed and refractory brain tumor patients is currently under way (NCT03328858).

4.2 | Caloric restriction diets

Similar to the ketogenic diet, other strategies attempt to “starve” tumor cells of glucose by decreasing overall caloric intake.¹¹⁵ This is a particularly worrisome strategy as starvation diets may deprive pediatric patients of essential micronutrients, cause weight loss and muscle wasting, and lead to impaired tolerability of chemotherapy.¹¹⁰ The utility of these diets has not been demonstrated in pediatric patients. Any benefit that may be derived by these types of diets must be weighed against the risks of malnutrition discussed above.

4.3 | Whole-food diets

Other dietary strategies attempt to use whole foods to prevent or treat cancers. For example, the macrobiotic diet endorses a predominantly vegetarian, whole-food diet. The evidence for the efficacy of this diet is lacking.¹¹⁶ However, encouraging a diet high in vegetables and whole grains is congruent with recommendations for a healthy diet provided by the American Institute for Cancer Research (www.aicr.org) and American Cancer Society (www.acs.org). Parents and patients should be counseled to ensure that any diet also adheres to recommended guidelines for pediatric nutrition and to recommendations specific to pediatric patients with cancer.

4.4 | Immune boosting and modulating diets

Another popular dietary strategy is the use of diets and supplements to “boost” the immune system, both to fight infections and to optimize the body’s own immune system against fighting cancer.^{117,118} Many websites and popular news articles in recent years have emphasized the role of particular foods in boosting the immune system (for example: <https://time.com/5313656/best-foods-for-immune-system/>). The largest academic body of work in this realm has been among adults requiring gastric surgeries, whereby enteral or parenteral nutrition is supplemented with immunonutrients such as arginine, glutamine polyunsaturated fatty acids, or others to optimize healing.¹¹⁹ Studies in the adult setting have demonstrated fewer infectious complications after cancer surgeries when patients were provided with enteral immunonutrition as compared with standard enteral or parenteral

nutrition.¹²⁰⁻¹²² However, immune modulating diets have not been studied in a rigorous manner in the pediatric cancer population, and further research is required.

5 | CONCLUSION

Many nutritional T&CM strategies exist and are used by pediatric patients with cancer and their families. Although these strategies are popular, rigorous studies of their safety and efficacy are often not available. Children with cancer should be encouraged to eat well-rounded diets that include fresh fruits and vegetables, whole grains, and proteins, to meet their dietary needs.¹²³ Given that no specific micronutrient has been found to offer specific benefit over others, it is likely that a well-rounded diet will provide adequate and safe amounts of the beneficial compounds found in food.

In many cases, such as with cannabinoids, public enthusiasm for integrative health strategies has outpaced current research. As such, further investigation of these agents, including clinical trials in children, is urgently required. Agents for study should be prioritized based on consultation with stakeholders, including families of children with cancer. Substances that are being used by families but that may also be associated with significant risk should be studied in a rigorous manner. For example, targeted studies of CBD oil and other cannabinoids that are being widely used by families but may cause significant adverse events are necessary. Agents that may be of benefit for supportive care or for curative purposes should also be prioritized. A global approach that includes Traditional Knowledge Holders may help identify priorities for research. For example, a recent article identified six different extracts from leaves demonstrating antitumor effects.¹²⁴ Research consortia, such as the COG, have the resources and expertise to continue to lead ongoing investigations of incorporating T&CM strategies into cancer care.

Nutritional status remains of crucial importance for all children, but particularly for children with cancer. Some nutritional T&CM strategies can be safely incorporated into pediatric cancer therapy, with careful research and collaborative discussion between providers and families.

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CONFLICTS OF INTEREST

The authors have no conflicts to disclose.

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