Support Care Cancer
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REVIEW ARTICLE

A systematic review of integrative clinical trials for supportive care in pediatric oncology: a report from the International Society of Pediatric Oncology, T&CM collaborative

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Abstract
Purpose Traditional and complementary medicine (T&CM) use in children with cancer is well established among high-income, upper middle-income, low-middle-income, and low-income countries (HIC, UMIC, LMIC, LIC, respectively). In HIC, a developing body of evidence exists for several T&CM therapies; however, evidence in other income settings is less well described despite a significantly higher use when compared to reports from HIC. The aim of this systematic review was to evaluate the evidence for T&CM for a variety of supportive care indications among children with cancer.
Methods We performed a systematic review following the PRISMA guidelines of randomized, controlled clinical trials from inception through September 2016. Our eligibility criteria were limited to T&CM studies performed in children and adolescents undergoing treatment for a pediatric malignancy.
Results Of 6342 studies identified, 44 met inclusion criteria. Two clinical trials reported on acupuncture, 1 reported on aromatherapy, 9 evaluated massage therapy, and 32 reported on dietary supplements. Twenty-two studies were performed in HIC, 15 in UMIC, and 7 in LMIC. T&CM therapies were most commonly investigated for the prevention or management of mucositis, weight loss, and febrile neutropenia. Encouraging results were reported for select interventions; however, the majority of studies were classified as poor to fair quality.
Conclusion Our search revealed numerous clinical studies investigating the use of T&CM for supportive care purposes in pediatric oncology in HIC, UMIC, and LMIC. Although limited, these results could inform supportive care resource allocation and indicate where T&CM may serve to fill gaps where access to care may be limited.

Keywords Traditional and complementary medicine · Integrative medicine · Pediatric oncology · Supportive care · Symptom management

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Background

The global incidence of childhood cancer has observed a steady increase in the last decade likely due to increased access to treatment and improved reporting of childhood cancer [1]. Traditional and complementary medicine (T&CM) is a globally utilized supportive care tool in children undergoing treatment for malignancies in countries of all income levels [2, 3]; however, there is a general consensus that the evidence supporting its efficacy remains unclear for most indications. The lack of demonstrated safety and efficacy, the potential for

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adverse interactions with prescribed therapy, the delays in seeking conventional treatment, and the risk of diminishing the high cure rate obtained for several pediatric malignancies have raised concerns about T&CM use [4–7].

T&CM has the potential be a low-cost adjunct to existing supportive care regimens and may be especially useful in low-middle-income countries (LMICs) where consistent access to supportive care medications may be limited [8]. There is a precedent of utilizing T&CM as a low-cost approach for closing gaps in medical care in LMICs, particularly in rural areas [9–12]. It is evident that additional research in T&CM is necessary prior to its inclusion into supportive care regimens in pediatric oncology. To this end, we describe the results of a systematic review of clinical trials that investigated the efficacy of T&CM therapies for supportive care indications in childhood cancer.

Methods

Literature search

Our methodology followed the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13]. Our search strategy included MeSH terms and text related to pediatrics, oncology, and T&CM (Online Resource 1). Our search was limited to studies of human subjects without any language restriction. All references were compiled into an EndNote (X7) library for review of titles and abstracts by two independent authors (AR and KT). Subsequent manual review of citations was performed with the inclusion of additional manuscripts that met the eligibility criteria below. Any disagreement was resolved by a final consensus (AR, KT, and EJL).

Eligibility criteria

Published manuscripts that reported on randomized, controlled, clinical trials that evaluated a T&CM therapy for supportive care purposes, performed among children and adolescents from birth to 18 years of age (inclusive), and diagnosed with a pediatric malignancy were included. Clinical trials that included adults were included in the systematic review if at least 80% of study participants were 18 years of age or younger. Classification of countries by income level was defined by criteria set forth by the World Bank [14]. Studies performed after cessation of cancer therapy, among children receiving surgery only, and case reports/case series/non-controlled trials were excluded. There was no exclusion by study date or date of publication.

Data extraction

Extracted data of interest included country of publication, year, demographic data (gender and age), diagnosis, study design, conventional cancer treatment, T&CM intervention (time in relation to phase of cancer therapy, dose, and duration of intervention), sample size, method of randomization, primary and secondary outcomes, statistical methods, and results. Data were extracted by one author (AR) and independently verified by a second author (EJL) using a standard data extraction sheet. Quality scores were calculated for eligible studies using the National Institute of Health's Quality Assessment Tool for Controlled Intervention Studies, a 14-point scale that identifies the quality of randomized, controlled trials (Online Resource 2) [15]. The criteria for assessing study quality were adapted from previously published studies [16, 17]. Two reviewers (AR and EJL) extracted data for determination of study quality.

Data synthesis and analysis

Due to the heterogeneity of the data and a small number of clinical trials evaluating a single T&CM therapy, a formal statistical analysis was not feasible. Study descriptives were extracted and summarized in table format (Tables 1, 2, 3, and 4). Within each table, studies were further classified by study outcomes and by the income level of the country in which the study was performed.

Results

Search strategy

A total of 6342 studies were produced in the original search (Fig. 1). Forty-seven papers from the original search met inclusion criteria. Of these, 16 studies were removed entirely due to inability to contact the author to clarify study details [18–33]. Thirty-one papers from the original search were included in the review. We identified an additional 56 manuscripts following the original literature search through reference review and ongoing monthly searches. Thirteen were eligible and included in the review [34–46]. Our final search results included 44 papers (acupuncture ($N = 2$), aromatherapy ($N = 1$), dietary supplements ($N = 32$), and massage ($N = 9$)).

Acupuncture

Two studies reported on acupuncture, both investigating the effect on chemotherapy-induced nausea and vomiting (Table 1), one of poor [47] and one of good [48] quality [47, 48]. Both studies were performed in high-income countries (HIC) and with a small, heterogeneous population. Each study

Table 1 Summary of studies in acupuncture

Outcome	Author	Income level	Diagnosis	Sample size	Gender/age	Study design	Cancer t therapy	Intervention	Results	Quality score
CINV	Gottschling (2008, Germany) [48]	HIC	Mixed	*N* = 23	13M, 10F, age = 13.6 ± 2.9 years	Multicenter randomized crossover study	VIDE, IP, I2VA, or I2VAd	Individualized acupuncture	↓ Antiemetic use ($P = 0.001$) ↓ Episodes of retching/ vomiting ($P = 0.01$)	Good
	Reindl (2006, Germany) [47]	HIC	Mixed	*N* = 11	4M, 7F, median age = 15.2 years (10–16.8 years)	Randomized, multicenter, prospective crossover trial	VIDE, IP, I2VA, or I2VAd	Acupuncture	↓ Antiemetic use ($P = 0.024$) Episodes of vomiting NS Nausea scores NS	Poor

CINV chemotherapy-induced nausea and vomiting, *F* females, *HIC* high-income country, *I2VA* vincristine, ifosfamide, actinomycin D, *I2VAd* vincristine, ifosfamide, adriamycin, *IP* ifosfamide, cisplatin, *M* males, *NS* non-significant, *VIDE* vincristine, ifosfamide, doxorubicin, etoposide

Table 2 Summary of studies in aromatherapy

Outcome	Author	Income level	Diagnosis	Sample size	Gender/age	Study design	Cancer therapy	Intervention	Results	Quality score
Anxiety	Ndao (2012, USA) [49]	HIC	Mixed	*N* = 37	Intrvn 13M, 4F, mean age = 11.7 ± 4.2 years; Ctrl 14M, 6F, mean age = 12.8 ± 5.6 years	Double-blind, placebo-controlled randomized study	Intrvn group: autologous HCT: *N* = 7 (41%); allogeneic HCT: *N* = 10 (59%); Ctrl group: autologous HCT: *N* = 7 (35%); allogeneic HCT: *N* = 13 (65%)	Bergamot essential oil	↑ State anxiety in the treatment group at T3 ($P = 0.01$) and T4 ($P = 0.05$) ↑ Nausea in intervention group at T3 ($P < 0.01$) and T4 ($P = 0.03$) ↑ Pain in intervention group at T1/T2 ($P = 0.04$)	Good

Ctrl control, *F* females, *HCT* hematopoietic cell transplant, *HIC* high-income country, *Intrvn* intervention, *M* males, *T* timepoint

Table 3 Summary of studies in massage

Outcome	Author	Income Level	Diagnosis	Sample Size	Gender/age	Study Design	Cancer Therapy	Intervention	Results	Quality Score
Nausea and vomiting	Mazlum (2013, Iran) [50]	UMIC	ALL	$N = 74$	Intrvn 60% M; Ctrl 51.4% M; mean age = 8.6 ± 3.3 years	2-group randomized controlled clinical trial study	CT	Swedish massage	↓ Incidence of nausea during 48 h post-chemo between groups ($P = 0.027$) ↓ Frequency of vomiting after therapy ($P = 0.001$) ↓ Duration of vomiting after therapy ($P = 0.002$) ↓ Severity of vomiting after therapy ($P = 0.002$) ↓ Frequency of total vomiting ($P = 0.014$) ↓ Duration of total vomiting ($P = 0.002$) ↓ Severity of total vomiting ($P = 0.011$)	Fair
	Miladinia (2015, Iran) [39]	UMIC	Mixed	$N = 45$	Intrvn 12M, 10F, mean age = 11.46 ± 2.14 years; Ctrl 13M, 8F, mean age = 10.91 ± 1.93 years	2-group randomized controlled double-blind trial, repeated measures design	CT	Slow-stroke back massage	↓ Nausea severity ($P = 0.001$) ↓ Frequency of vomiting ($P = 0.001$)	Fair
Pain	Batalha (2013, Portugal) [51]	HIC	Mixed	$N = 52$	Intrvn 76.9% M, median = 13.5 years; Ctrl 46.2% M, median age = 12 years	Prospective, longitudinal, randomized, controlled and single-blinded study	CT, antibiotics, or steroid corticoid therapy	Massage	↓ Pain interference with ambulatory capacity between days 1 and 6 ($P < 0.05$)	Poor
Psychosocial outcomes	Field (2001, USA) [56]	HIC	ALL	$N = 20$	10M, 10F, mean age = 6.9 years	Randomized, wait-list control	Standard medical care (medical exams, RT, CT, other medical procedures)	Parent-administered massage	↓ Parental anxiety ($P = 0.05$) ↓ Parental depressed mood ($P = 0.01$) ↓ Child anxiety ($P = 0.05$) ↓ Child depressed mood ($P = 0.01$) ↑ WBC ($P = 0.05$) ↑ Neutrophils ($P = 0.05$)	Poor
	Haun (2009, USA) [55]	HIC	Mixed	$N = 30$	Intrvn 8M, 7F, mean age = 10.7 years; Ctrl 7M, 8F, mean age = 9.3 years	Randomized, non-blinded, prospective study	NR	Swedish massage	↓ Muscle soreness ($P < 0.001$) ↓ Discomfort ($P < 0.001$) ↓ Respiratory rate ($P < 0.000$) ↓ Anxiety ($P < 0.000$)	Poor

Table 3 (continued)

Outcome	Author	Income Level	Diagnosis	Sample Size	Gender/age	Study Design	Cancer Therapy	Intervention	Results	Quality Score
									Improvement in emotional symptoms ($P < 0.001$) Improvement in clinical progress score ($P < 0.001$)	
Psychosocial outcomes (cont'd)	Phipps (2005, USA) [40]	HIC	Mixed	$N = 50$	20% < 6 years, 46% 6–12 years, 34% > 12 years	Randomized trial	Allogeneic HCT: $N = 38$, autologous HCT: $N = 12$	Professional or parent massage	↓ Child ($P = 0.004$) and parent ($P < 0.0001$) reported anxiety with professional massage ↓ Parent-reported discomfort ($P = 0.004$) with professional massage ↓ Days to engraftment in parent massage vs. control ($P = 0.04$)	Poor
	Phipps (2010, USA/Canada) [52]	HIC	Mixed	$N = 178$	59.1% M; 49.1% 6–12 years, 50.9% > 12 years	Multisite, prospective, controlled trial	Autologous HCT: $N = 31$ (18.1%), allo-matched sibling HCT: $N = 44$, 25.7%, allo-other HCT: $N = 96$, 56.1%	Massage and humor therapy	No significant findings	Fair
	Phipps (2012, USA) [53]	HIC	Mixed	$N = 171$	59.1% M, mean age = 12.8 years (6–18 years)	Randomized, multisite trial	Autologous HCT 18.1%, allogeneic-matched sibling HCT 25.7%, allogeneic-other HCT 56.1%	Massage and humor therapy	No significant findings	Poor
	Post-White (2009, USA) [54]	HIC	Mixed	$N = 25$	60% M, age range 1–18 years	Crossover	CT	Massage therapy vs. quiet time	↓ HR ($P = 0.02$) ↓ RR ($P = 0.05$) ↓ Anxiety in children 1–13 at session 4 ($P = 0.04$) Salivary cortisol NS	Poor

ALL acute lymphoblastic leukemia, *cont'd* continued, *CT* chemotherapy, *Ctrl* control, *F* females, *HIC* high-income country, *HR* heart rate, *Intrvn* intervention, *M* males, *NS* non-significant, *RR* relative risk, *RT* radiation therapy, *UMIC* upper middle-income country, *WBC* white blood cell

Table 4 Summary of studies in dietary supplements

Outcome	Author	Income level	Diagnosis	Sample size[a]	Gender/age	Study design
Appetite/weight management	Bayram (2009, Turkey) [35]	UMIC	Mixed	$N = 52$	Intrvn 63.6% M, Ctrl 52.6% M; mean age = 7.5 ± 3 years	Prospective, randomized, controlled, single-center, open-label design
	Consolo (2013, Brazil) [70]	UMIC	Mixed	$N = 38$	53% M; mean age = 9.9 ± 5.5 years	Double-blind, randomized, placebo-controlled trial
	Naderi (2014, Iran) [71]	UMIC	ALL	$N = 34$	Intrvn 3M, 14F; mean age = 5.79 ± 3.97 years (1–13 years); Ctrl 11M, 6F, mean age = 7.17 ± 3.66 years (6 months–14 years)	Randomized controlled trial
Bone mineral density	Diaz (2008, Chile) [76]	HIC	ALL	$N = 16$	9M; mean age = 5.5 years (1.7–11.5 years)	Non-blinded, quasi-randomized trial
CINV	Pillai (2011, India) [75]	LMIC	Newly diagnosed bone sarcomas	$N = 60$	Intrvn 24M, median age = 15.5 years (9–21 years); Ctrl 16M, median age = 15.83 years (9–21 years)	Prospective, double-blind, randomized, controlled, single institutional trial
CINV (cont'd)	Shi (2012, China) [74b]	UMIC	Mixed	$N = 80$	Intrvn 20M, 20F, mean age = 3.0 ± 1.8 years; Ctrl 26M, 14F, mean age = 4.0 ± 2.3 years	Not reported
Fever and neutropenia	Abdulrhman (2016, Egypt) [38]	LMIC	ALL	$N = 40$	50% M; group A mean age = 5.1 ± 2.5 years (2.5–10 years); group B mean age = 5.65 ± 2.24 years (2.5–10 years)	Open-label, randomized crossover clinical trial
	Garami (2004, Hungary) [73]	HIC	Mixed	$N = 22$	8M; Intrvn mean age = 11 years (2–17 years); Ctrl mean age = 10.6 years (2–18)	Open-label, matched-pair pilot clinical trial
	Wada (2010, Japan) [45]	HIC	Mixed	$N = 42$	Intrvn 7M, 11F, 1 year 2 months–13 years 2 months (mean/median age not specified); Ctrl 9M, 13F, 1 year 1 month—13 years 4 months (mean/median age not specified)	Single-blinded, placebo-controlled trial
Fever and neutropenia (cont'd)	Wada (2010, Japan) [45] (cont'd)					
Gastrointestinal	Dagdemir (2004, Turkey) [77]	UMIC	Mixed	$N = 35$	Intrvn 12M, 10F, median age = 8.7 years (3–16 years); Ctrl 8M, 5F, median age = 9.2 years (2.5–16 years)	Randomized, otherwise not reported
Hepatic toxicity	Elbarbary (2016, Egypt) [41]	LMIC	ALL	$N = 70$	Intrvn 18M, 17F, mean age = 8.4 ± 3.3 years (4–16 years); Ctrl 21M, 14F, mean age = 7.1 ± 3.1 years (3–15 years)	Double-blind, randomized placebo-controlled trial
	Hagag (2015, Egypt) [42]	LMIC	ALL	$N = 40$	Intrvn 15M, 5F, mean age = 8.84 ± 3.56 years (5–12 years); Ctrl 13M, 7F, mean age = 9.34 ± 3.28 years (4–13 years)	Randomized controlled trial
Hepatic toxicity (cont'd)	Ladas (2010, USA) [72]	HIC	ALL	$N = 50$	58% M; Intrvn mean age = 8.7 ± 5.1 years; Ctrl mean age = 7.0 ± 3.2 years	Randomized, controlled, double-blind pilot trial
Mucositis	Abdulrhman (2012, Egypt) [34]	LMIC	ALL	$N = 90$	57M; mean age = 6.9 ± 3.8 years (2–18 years)	Randomized controlled clinical phase II trial
	Aquino (2005, USA) [57]	HIC	Mixed	$N = 120$		Double-blind randomized placebo-controlled trial

Table 4 (continued)

Outcome	Author	Income level	Diagnosis	Sample size[a]	Gender/age	Study design
					Intrvn 65% M, mean age = 8.9 ± 1 years; Ctrl 57% M, mean age = 10.5 ± 0.6 years	
	El-Housseiny (2007, Egypt) [36]	LMIC	NR	*N* = 80	Group A (topical vit. E) mean age = 5.75 years; group B (systemic vit. E) mean age = 9.30 years	Prospective randomized trial
Mucositis (cont'd)	Khurana (2013, Turkey) [58]	UMIC	Mixed	*N* = 72	Group 1 19M, 5F, mean age = 8.98 ± 2.58 years; group 2 (vit. E) 18M, 6F, mean age = 9.29 ± 2.58 years; group 3 (pycnogenol): 20M, 4F, mean age = 9.48 ± 2.53 years	Single-blind controlled trial
	Kokkonen (2002, Finland) [59]	HIC	Mixed	*N* = 20	Intrvn 5M, 5F, mean age = 7.7 ± 4.4 years; Ctrl 5M, 5F, mean age = 8.7 ± 5.2 years	Prospective, randomized trial
	Oberbaum (2001, Israel) [37]	HIC	Mixed	*N* = 30	Intrvn 53% M, mean age = 10.1 ± 7.0 years; Ctrl 60% M, mean age = 9.7 ± 5.7 years	Randomized, placebo-controlled, double-blind clinical trial
	Okur (2006, Turkey) [60]	UMIC	Mixed	*N* = 21	Mean age = 9.86 ± 5.38 years	Crossover trial
	Sencer (2010, USA) [61]	HIC	Mixed	*N* = 195	Intrvn 56% M, median age = 12 years (3–24 years); Ctrl 70% M, median age = 11 years (3–25 years)	International multicenter, double-blind, placebo-controlled randomized trial
Mucositis (cont'd)	Sung (2007, Canada) [65]	HIC	Mixed	*N* = 16	Median age = 12.7 years (6.4–15.1 years)	Series of *N* of 1, double-blinded, randomized controlled trials
	Tomazevic (2013, Slovenia) [62]	HIC	Mixed	*N* = 50	Intrvn 11M, 8F, mean age = 6.7 ± 5.3 years (1.0–16.8 years); Ctrl 9M, 12F, mean age = 9.3 ± 6.6 years (1.0–18.8 years)	Double blind, randomized, placebo-controlled trial
	Uderzo (2011, Italy) [63]	HIC	Mixed	*N* = 120	Intrvn 70% M, mean age = 8.0 years (0.9–18.6 years); Ctrl 67.2% M, mean age = 8.4 years (0.4–18.6 years)	Prospective, randomized, double-blind, controlled trial
	Yildirim (2013, Turkey) [64]	UMIC	B cell non-Hodgkin lymphoma	*N* = 12	10M, 2F; median age = 72 months (48–120 months)	Crossover trial
Neurotoxicity	Bradfield (2015, USA) [43]	HIC	Mixed	*N* = 250	Intrvn: stratum 1 14M, 12F, mean age = 9.1 ± 5.6 years, stratum 2 67M, 34F, mean age = 8.4 ± 4.7 years; Ctrl: stratum 1 12M, 11F, mean age = 8.8 ± 5.5 years, stratum 2 57M, 42F, mean age = 8.5 ± 4.8 years	Randomized, placebo-controlled, double-blind clinical trial
Neurotoxicity (cont'd)	Mokhtar (2010, Egypt) [44]	LMIC	Mixed	*N* = 94	Intrvn 37M, 17F, mean age = 7.42 ± 3.85 years; Ctrl 30M, 10F, mean age = 6.78 ± 4.21 years	Randomized, single-blinded, placebo-controlled clinical trial
Treatment-related toxicities	Tacyildiz (2010, Turkey) [66]	UMIC	Mixed	*N* = 8	3M, median age = 7 years (6–13 years)	Crossover trial
	Rocha (2016, Brazil) [46]	UMIC	Mixed	*N* = 34	LL group 10M, 7F, mean age = 7.6 years; ST group 13M, 6F, mean age = 8.0 years	Randomized, double-blind, placebo-controlled, crossover trial
Treatment-related toxicities (cont'd)	Shi (2007, China) [68]	UMIC	Mixed	*N* = 60	Intrvn 19M, 11F, mean age = 4.43 ± 2.47 years; Ctrl 20M, 10F, mean age = 2.80 ± 1.69 years	Prospective cohort trial
	Shi (2012, China) [67a]	UMIC	Mixed	*N* = 167	Intrvn 45M, 38F, mean age = 3.7 ± 2.3 years; Ctrl 48M, 36F, mean age = 3.83 ± 2.61 years	NR
Treatment-related toxicities (cont'd)	Shi (2012, China) [67a] (cont'd)					

Table 4 (continued)

Outcome	Author	Income level	Diagnosis	Sample size[a]	Gender/age	Study design
	Vieira (2015, Brazil) [69]	UMIC	Mixed	$N = 39$	LL group 10M, 9F, mean age = 8.2 years; ST group 12M, 8F, mean age = 7.4 years	Randomized, double-blind, placebo-controlled, phase II crossover trial

Outcome	Cancer therapy[b]	Supplement/dose	Results	Quality Score
Appetite/weight management	CT	Protein and energy-dense EPA-containing oral supplement; 300 kcal, 16 g protein, 1.09 g EPA twice a day	↓ Loss of body wt ($P = 0.001$) and loss of BMI ($P = 0.002$) at 3 months↓ Weight loss at 6 months ($P = 0.03$)↓ Body wt loss ($P = 0.006$) and BMI loss ($P = 0.018$)↑ Remission rate at 3 months ($P = 0.036$)	Fair
	CT	Zinc chelate; 2 mg/kg/day of zinc (max 60 mg/day)	↑ Weight gain ($P = 0.032$)Significant difference between group A and group B regarding infectious episodes was observed ($P = 0.02$)	Fair
	CT	PediaSure (100–150 cm^3 every other day) and carnitine (50 mg/kg everyday)	NS effect on anthropometric measures	Good
Bone mineral density	Protocol 1 PINDA phase 1	Calcitriol (< 30 kg: 0.25 mg/day; > 30 kg: 0.5 mg/day)	↑ Lumbar spine BMD in children with lower initial BMD in the calcitriol group vs. higher initial BMD ($r = -0.78$, $P = 0.020$)	Poor
CINV	Combination of cisplatin 40 mg/m^2/day and doxorubicin 25 mg/m^2/day	Ginger root powder (≥ 20 and < 40 kg: 1000 mg; ≥ 40 and < 60 kg: 2000 mg)	↓ Moderate to severe nausea ($P = 0.003$)↓ Moderate to severe vomiting ($P = 0.002$)↓ Moderate to severe delayed nausea ($P < 0.001$)↓ Moderate to severe delayed vomiting ($P = 0.022$)	Good
CINV (cont'd)	CT	Hewei Zhiou Recipe (fresh common reed rhizome 30 g, fresh bamboo shavings 4–6 g, fresh ginger 3 pieces, Chinese date 3 pieces)	↓ Vomiting by end of second to sixth therapeutic course ($P < 0.01$)	Fair
Fever and neutropenia	Modified CCG 1991 protocol for standard-risk ALL and on maintenance therapy	Honey (2.5 g/kg body wt, twice weekly)	↓ Number of patients with FN ($P = 0.037$) ↓ FN episodes ($P = 0.004$) ↓ Duration of hospital stay ($P = 0.006$) ↓ Number of patients who developed FN during intervention ($P = 0.00004$)	Fair
	Cerebral PNET: carboplatin, cyclophosphamide, dactinomycin, doxorubicin, epirubicin, etoposide, ifosfamide, vincristine; osteosarcoma: carboplatin, cisplatin, doxorubicin, ifosfamide, methotrexate; hepatoblastoma: cisplatin, doxorubicin; mesenchymal chondrosarcoma: cyclophosphamide, doxorubicin, etoposide, ifosfamide, vincristine	Avemar (6 g/m^2 dissolved in water, twice daily)	↓ Neutropenic episodes ($P = 0.037$)↑ WBC counts ($P < 0.021$)↑ Lymphocyte counts ($P < 0.001$)	Fair
	CT	Bifidobacterium breve strain Yakult (10^9 in 1 g preparation, 3 times per day)	↓ Frequency ($P = 0.02$) and duration ($P = 0.02$) of febrile episodes ↓ Proportion of patients who developed fever (RR 0.65) ↓ Cumulative length of parenteral antibiotic therapy ($P = 0.04$)	Fair

Table 4 (continued)

Outcome	Cancer therapy[b]	Supplement/dose	Results	Quality Score
Fever and neutropenia (cont'd)			↓ Proportion of those who used parenteral antibiotic (RR 0.75)	
Gastrointestinal	HDMTX	Vitamin A (180,000 IU/day)	↓ D-Xylose absorption in control vs. intervention ($P = 0.033$)↓ D-Xylose in control group with lower RBP at baseline compared to trial group ($P = 0.004$)	Poor
Hepatic toxicity	MTX-including treatment protocols	Omega-3 fatty acids (1000 mg fish oil—180 mg EPA, 120 mg DHA)	↓ Total and direct bilirubin, ALT, AST, ALP, GGT, MDA ($P < 0.001$) ↑ Uric acid ($P = 0.004$) ↑ TAC, SOD, and GPX ($P < 0.001$)	Good
	MTX-including treatment protocols	Black seed oil (80 mg/kg/day)	↓ Total ($P = 0.000$) and direct ($P = 0.000$) bilirubin ↓ Indirect bilirubin ($P = 0.000$) ↓ Serum ALT ($P = 0.000$) ↓ Serum AST ($P = 0.000$) ↓ Alkaline phosphatase ($P = 0.000$) ↓ Prothrombin time ($P = 0.01$) ↓ Relapse and death ($P = 0.029$) ↑ Complete remission ($P = 0.029$)	Fair
Hepatic toxicity (cont'd)	MTX, 6-MP, VCR	Milk thistle (1:2 mixture of silibinin and soy phosphatidylcholine); 240 mg milk thistle (80 mg silibinin)	↓ AST ($P = 0.04$)5 patients in MT group and no patients in placebo group had greater than a 50% reduction in total bilirubin during intervention period ($P < 0.007$)	Good
Mucositis	BFM-90 (standard risk, consolidaton phase)	Honey; 0.5 g/kg (max 15 g) 3 times daily × 10 days or until healedHOPE; 0.25 g/kg 3 times daily × 10 days or until healed vs. controls (benzocaine gel)	↓ Grade 2 mucositis recovery time in honey group ($P < 0.05$)↑ Grade 3 mucositis healing time in honey and HOPE vs. control ($P < 0.01$) ↑ Healing time with honey alone in grades 2 and 3 mucositis vs. control ($P = 0.0005$) or HOPE ($P = 0.0056$)	Fair
	Autologous or allogeneic HCT with TBI or MTX	Glutamine; 2 g/m^2/dose (max 4 g); twice daily	↓ Morphine use ($P = 0.03$)↓ TPN use ($P = 0.01$)	Good
	CT	Vitamin E; 100 mg twice daily	No significant findings	Poor
Mucositis (cont'd)	ALL: induction or delayed intensification; AML: induction or intensification; NHL: MCP-842	Vitamin E; 200 mg/day, 3 times daily × 1 weekPycnogenol; 1 mg/kg per day, 3 times daily × 1 week	↑ Number of patients who healed completely with vitamin E than pycnogenol or control (*P* value NR) Significant difference in WHO mucositis grading between group 1 (control) and group 2 (vit. E) ($P < 0.0001$)	Fair
	Protocol of the NSPHO; MOPP, ABVD; LBM-89, BFM-90; IRS-III; NWTS-4	Vitamin A; 10 mg/kg × first 3 weeks, 5 mg/kg × next 3 weeks	No significant findings	Fair
	Allogeneic or autologous HCT	Traumeel S; 2.2 mL five times daily	↓ Symptom duration and severity ($P < 0.01$)↓ Time to worsening of symptoms ($P < 0.001$)	Good
	BEP; BB24, CC, mini-BEAM; ABVD; A3; P-IV; HDMTX; EVAII; HTP	Glutamine; 4 g/m^2/day	NS differences between gln course and non-gln course on first and fifth days↓ Need for antibiotic therapy in gln group vs. control ($P = 0.03$)	Poor
	Myeloablative HCT (allogeneic or autologous)	Traumeel S; 2.2 mL five times daily	Trend towards ↓ narcotic use in Traumeel group ($P = 0.02$) No other significant findings	Good
Mucositis (cont'd)	Doxorubicin-containing CT	Topical vitamin E 800 mg	No significant findings	Good

Table 4 (continued)

Outcome	Cancer therapy[b]	Supplement/dose	Results	Quality Score
	CT	Propolis; 0.38 g twice daily	No significant findings	Fair
	Allogeneic HCT	Glutamine; 0.4 g/kg/day	No significant findings	Good
	BFM-90	Glutamine; 0.4 g/kg/day	No significant findings	Fair
Neurotoxicity	Stratum1: VCR; Stratum 2: VCR + steroids	L-Glutamic acid (250 mg capsules, 1 capsule for body surface < 1 m^2, 2 capsules for ≥ 1 m^2; 3 times daily	No significant findings	Fair
Neurotoxicity (cont'd)	VCR	Glutamic acid (1.5 g daily in 3 divided doses)	↓ Reduction of tendon Achilles reflex at third ($P = 0.01$) and fourth visits ($P = 0.004$) ↓ Reduction in patellar reflex at third and fourth visits ($P = 0.008$) ↓ Paresthesias ($P = 0.01$) ↓ Constipation ($P = 0.02$) ↓ Rate of constipation development (P value NR) ↓ Neurotoxicity sum score at second ($P = 0.01$), third ($P = 0.000$), and fourth ($P = 0.000$) visits Changes in anxorexia and strength NS	Fair
Treatment-related toxicities	ICE, A5, A3, ACC, VCR-carbopolatin, CTX, paclitaxel, paclitaxel + RT, irinotecan + temozolamide, temozolamide + COPP + VCR-carboplatin, irinotecan + RT	Genistein (0.30 g/tablet: 82% soy isoflavone extract + 2.7% (8 mg) genistein)	No significant findings	Poor
	CT	Selenium glycinate (0–6 months, 27 μg/day, 7–12 months, 36 μg/day, 1–3 years, 36 μg/day, 4–8 years, 54 μg/day, 9–13 years, 72 μg/day, 14–18, 100 μg/day	↑ Neutrophil count in ST group ($P = 0.0192$) ↑ IgA ($P = 0.0051$) and IgG ($P = 0.0055$) in ST vs. LL patients after Se use ↑ IgA production after Se in ST vs. LL group ($P = 0.0011$)	Poor
Treatment-related toxicities (cont'd)	CT ± RT: phase II: VCR, CTX, ADM, ACTD, 5-FU; phases III and IV: VCR, CTX, ADM, DDP, Vp16, BLM	Various Chinese herbs according to syndrome differentiation (decocted twice, 50 mL per time for children < 3 years, 100 mL per time for children > 3 years, BID	↑ WBC ($P < 0.01$) ↓ PLT ($P < 0.05$) ↓ Clinical symptom scores ($P < 0.01$)	Fair
	Phase II: VCR, CTX, ADM, ACTD, 5-FU; phases III and IV: VCR, CTX, ADM, DDP, Vp16, BLM	Fuzheng Jianpi Decoction (50–100 mL BID)	↓ Nausea and vomiting at 6 months ($P = 0.001$) and 1 year ($P = 0.001$) ↓ Anorexia at 6 months ($P = 0.000$) and 1 year ($P = 0.000$) ↓ Weakness at 6 months ($P = 0.014$) and 1 year ($P = 0.001$) ↓ Weight loss at 6 months ($P = 0.003$) and 1 year ($P = 0.017$) ↓ Constipation at 6 months ($P = 0.002$) ↓ Pain at 1 year ($P = 0.04$ ↓ 2 and 3-year psychological ($P < 0.05$) and general symptom scores ($P < 0.01$) compared with 1 year ↓ 2 and 3-year somatic and psych functions and general symptom scores (all $P < 0.05$)	Fair

Table 4 (continued)

Outcome	Cancer therapy[b]	Supplement/dose	Results	Quality Score
Treatment-related toxicities (cont'd)	CT	Selenium (0–6 months = 27 μg/day; 7–12 months 36 μg/day; 1–3 years= 36 μg/day; 4–8 years = 54 μg/day; 9–13 years = 72 μg/day; 14–18 years = 100 μg/day)	↓ 2-year somatic and psych functions ($P < 0.05$) ↓ 3-year psych functions and general symptoms scores ($P < 0.05$) ↑ WBC ($P < 0.01$) and Hb ($P < 0.05$) at 6 months ↑ WBC ($P < 0.01$) and PLT ($P < 0.05$) at 1 year ↑ Physical function ↓ Nausea ($P = 0.0036$) and appetite loss ($P = 0.028$) in ST group ↓ Fatigue in ST group at 1 year ($P = 0.0289$) ↓ AST ($P = 0.0447$) ↓ Serum creatinine ↓ Serum urea	Fair

μg micrograms, *5-FU* 5-fluorouracil, *6-MP* 6-mercaptopurine, *A3* vincristine, adriamycin, dacarbazine, iphosphamide, *A5* cisplatin, cyclophosphamide, etoposide, *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine, *ACC* adriamycin, cisplatin, etoposide, mitotane, *ACTD* dactinomycin, *ADM* adriamycin, *ALL* acute lymphoblastic leukemia, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AML* acute myeloid leukemia, *AST* aspartate aminotransferase, *BB24* dexametasone, vincristine, methotrexate, cyclophosphamide, doxorubin, *BEP* bleomycin, etoposide, cisplatin, *BFM-90* Berlin-Frankfurt-Munster protocol, *BID* twice a day, *BLM* bleomycin, *BMD* bone mineral density, *BMI* body mass index, *CC* dexametosone, vincristine, citarabine, vepeside, *cc* cubic centimeters, *CCG 1991* Children's Cancer Group 1991, *cont'd* continued, *COPP* cyclophosphamide, vincristine, procarbazine, prednisone, *CT* chemotherapy, *Ctrl* control, *CTX* cyclophosphamide, *DDP* cisplatin, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *EVAII* etoposide, vincristine, adriamycin, iphosphamide, *F* females, *FN* febrile neutropenia, *g* grams, *GGT* gamma-glutamyl transpeptidase, *GPX* glutathione peroxidase, *Hb* hemoglobin, *HCT* hematopoietic cell transplant, *HDMTX* high-dose methotrexate, *HIC* high-income country, *HOPE* honey, olive oil-propolis extract and beeswax, *HTP* cisplatin, adriamycin, *gln* glutamine, *ICE* ifosfamide, carboplatin, etoposide, *IgA* immunoglobulin A, *IgG* immunoglobulin G, *Intrvn* intervention, *IRS-III* Third Intergroup Rhabdomyosarcoma Study, *IU* international units, *LBM-89* Lymphome Malins de Burkitt, *LL* leukemia/lymphoma, *LMIC* low-middle-income country, *kcal* kilocalories, *kg* kilograms, *M* males, *m* meters, *max* maximum, *MCP-842* mitoxantrone, chlorambucil, prednisolone, *MDA* malondialdehyde, *mg* milligrams, *mini-BEAM* carumustine, etoposide, citarabine, melphalan, *mL* milliliters, *MOPP* mustargen oncovin procarbazine prednisone, *MT* milk thistle, *MTX* methotrexate, *NHL* non-Hodgkin lymphoma, *NR* not reported, *NS* non-significant, *NSPHO* Nordic Society for Pediatric Hematology and Oncology, *NWTS-4* National Wilms' Tumor Study-4, *P-IV* actinomycin, vincristine, *PINDA* Programa Infantil de Drogas Antineoplásicas de Chile, *PLT* platelets, *PNET* primitive neuroectodermal tumor, *RBP* retinol-binding protein, *RR* relative risk, *RT* radiation therapy, *Se* selenium, *SOD* superoxide dismutase, *ST* solid tumor, *TAC* total antioxidant capacity, *TBI* total body irradiation, *TPN* total parenteral nutrition, *UMIC* upper middle-income country, *VCR* vincristine, *vit*. vitamin, *Vp16* etoposide, *WBC* white blood cell, *WHO* World Health Organization, *wt* weight

[a] Sample size = number randomized

[b] When indicated, protocol provided in table. Otherwise chemotherapy ± radiation

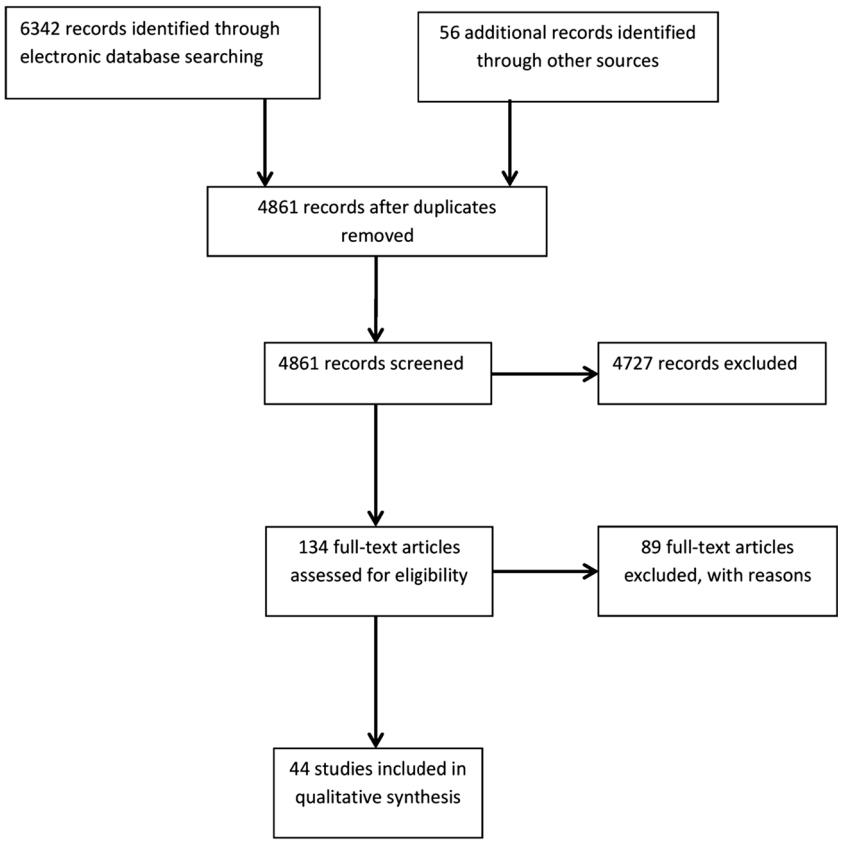

Fig. 1 Results of search strategy

reported a significant decline in the use of antiemetics. One study reported a significant decrease in episodes of retching and/or vomiting [48].

Aromatherapy

One good-quality study investigated aromatherapy among children undergoing hematopoietic stem cell transplantation (HCT) (Table 2) [49]. This trial, performed in an HIC, examined the effects of bergamot essential oil on anxiety in 27 children undergoing HCT for a variety of diagnoses. The authors found increased nausea and anxiety in the aromatherapy group compared with the control group.

Massage

Nine studies, all performed in HIC and upper middle-income countries (UMIC), investigated the use of massage (Table 3) [39, 40, 50–56]. Six studies were of poor quality [40, 51, 53–56], and three were of fair quality [39, 50, 52]. Massage was administered in the inpatient [40, 50–55] and outpatient [54, 55] setting and at home [56]. One paper did not report the setting [39]. Various forms of massage therapy were provided and included massage therapy provided by parents [56], registered nurses [51], and licensed massage therapists [40, 50, 52–55]. One study did not report the provider of massage therapy [39]. Six of the studies examined the effect of massage on psychosocial outcomes [40, 52–56] and three studies on symptom management [39, 50, 51]. Three of the trials demonstrated a statistically significant reduction in child's anxiety [40, 54, 56]. One study found that Swedish massage was effective at reducing nausea and vomiting during 48 h post chemotherapy ($P = 0.027$) [50], and another found that slow-stroke back massage reduced nausea severity and vomiting frequency over the course of six chemotherapy infusions [39]. A third found that massage therapy reduced pain [51]. Swedish massage provided in the inpatient and outpatient settings reported beneficial effects on muscle soreness, discomfort, respiratory rate, anxiety, emotional symptoms, and clinical progress scores [55].

Supplements

Thirty-two studies investigated the use of dietary supplements for several supportive care indications (Table 4). Twelve studies examined the effects of dietary supplements on mucositis, [34, 36, 37, 57–65], five studied treatment-related toxicities [46, 66–69], three examined appetite and weight management [35, 70, 71], three evaluated hepatic toxicity [41, 42, 72], three evaluated fever and neutropenia [38, 45, 73], two studies evaluated neuropathy [43, 44], two examined chemotherapy-induced nausea and vomiting [74, 75], and one study each

examined bone mineral density [76] and gastrointestinal symptoms [77]. Of the 32 studies, 12 studies were performed in HIC [37, 43, 45, 57, 59, 61–63, 65, 72, 73, 76], 13 in UMIC [35, 46, 58, 60, 64, 66–71, 74, 77], and 7 in LMICs [34, 36, 38, 41, 42, 44, 75]. Seven papers received a quality score of "poor" [36, 46, 60, 66, 76, 77], 17 "fair" [34, 35, 38, 42–45, 58, 59, 62, 64, 67–70, 73, 74], and 9 "good" [37, 41, 57, 61, 63, 65, 71, 72, 75]. Most studies included a wide range of diagnoses with few studies performed among homogenous patient populations.

The use of dietary supplements for the prevention or treatment of mucositis was the most commonly investigated supportive care indication. Glutamine ($N = 4$) was the most widely studied supplement for this indication; however, variable doses, routes, and duration were studied (Table 4) [57, 60, 63, 64]. Two studies were performed in children undergoing HCT; one showed decreased use of morphine and TPN in children receiving glutamine [57], and the other showed no benefit [63]. The other two studies found decreased antibiotic use in the glutamine group [60], while the other reported no significant findings [64].

Three studies evaluated vitamin E for the prevention [65] and treatment [36, 58] of mucositis. One study found a significant improvement in mucositis scores [58]; the other two reported no significant findings [36, 65]. Vitamin A was evaluated for the prevention of mucositis and did not report significant results [59]. Finally, honey was found to reduce the recovery time of mucositis when compared to a mixture of honey, olive oil-propolis extract and beeswax, or control [34]. The use of propolis, a bee resin, alone did not produce any significant results [62]. The first T&CM clinical trial conducted through Children's Oncology Group (COG) [61] administered Traumeel S or placebo to 200 children undergoing HCT. The authors did not find a significant effect on mucositis; however, a trend in the reduction in the administration of narcotics was observed.

Several studies examined T&CM therapies for a variety of treatment-related toxicities. Genistein [66] did not report significant effects, whereas beneficial effects were observed for selenium [46, 69]. One study examined Fuzheng Jianpi Decoction, a mixture of several different herbal remedies, and found improvement in anorexia, weakness, weight loss, constipation, pain, and somatic and psychological functioning [67]. Another study found a benefit on white blood cell (WBC) count and clinical symptom scores with various and individualized Chinese herbs [68].

Three studies addressed appetite and weight management [35, 70, 71]. Zinc chelate (2 mg/kg/day) significantly prevented weight loss, while also decreasing the number of infectious episodes [70]. An energy-dense eicosapentaenoic acid supplement (1 g BID) significantly decreased loss of body weight and body mass index [35]. A study evaluating PediaSure® and carnitine revealed no significant impact on anthropometric measures [71].

Three studies evaluated hepatic toxicity [41, 42, 72]. A small, multicenter pilot study found that milk thistle significantly decreased aspartate aminotransferase (AST) and total bilirubin among children with acute lymphoblastic leukemia in the maintenance phase of therapy [72]. Omega-3 fatty acids were found to reduce liver enzymes and increase antioxidants and uric acid [41]. Another study found that black seed oil decreased liver enzymes, alkaline phosphatase, and prothrombin time [42].

A study found that wheat germ extract significantly decreased neutropenic episodes and improved WBC and lymphocyte counts [73]. A Japanese study found that probiotics reduced the frequency and duration of febrile episodes and lowered the risk of developing fever [45]. In another study, administration of honey was associated with a reduction in the number of episodes of fever, number of children who developed febrile neutropenia, and reduced duration of hospital stays [38].

Glutamic acid was evaluated for neurotoxicity in two studies [43, 44]. One study found reduced severity of the tendon Achilles and patellar reflexes and decreased paresthesias, constipation, and neurotoxicity summary score [44]. In contrast, a multicenter consortium group study found that glutamic acid was not effective in the prevention of vincristine-induced neurotoxicity [43].

Two studies found improvement in nausea and vomiting with dietary supplements [74, 75]. A study examining vitamin A for D-xylose malabsorption found no significant effects [77]. Supplementation with calcitriol was found to improve lumbar spine bone mineral density [76].

Discussion

To the authors' knowledge, we present the results from the first systematic review of clinical trials investigating T&CM interventions for supportive care indications in children and adolescents with cancer. Within each of the T&CM domains, the reported findings conflicted, identifying opportunities to further advance each of these domains within pediatric oncology. The widespread and persistent use of T&CM, particularly in LMICs, further endorses the need for additional research in pediatric oncology [3, 78, 79].

Several of the reviewed studies investigated the efficacy of massage therapy, a generally safe and accepted T&CM intervention [80]. We found encouraging evidence suggesting that massage therapy may be beneficial for several symptoms, which concurs with a recent consensus statement on non-pharmacologic approaches [81]. Evidence-based, non-pharmacologic T&CM interventions may be a cost-effective

approach to advance the provision of supportive and palliative care across all income settings.

The role of acupuncture has been one of the most thoroughly researched T&CM modalities with some translational data describing its role for the treatment of several disorders [82–86], including chemotherapy-induced nausea and vomiting and pain management [87]. Our review found that there are a limited number of studies in pediatric oncology despite documented safety and feasibility in pediatric oncology [88–90]. Acupuncture may be especially beneficial for clinicians, children, and adolescents seeking non-pharmacologic approaches to manage a specified indication or symptom clusters. Training and licensing guidelines set forth by HIC or countries with an established system for delivering Traditional Chinese Medicine may serve as a framework for the investigation of acupuncture in countries without an established body of legislation.

Our review found that the largest number of T&CM studies evaluated the role of a dietary or herbal supplement for symptom management. The role of dietary supplements has been one of the most controversial aspects of T&CM due to the risk of adverse interactions with cancer therapy together with the absence of governing bodies providing oversight on the manufacturing and processing of dietary supplements. We found that two large cooperative groups conducted multicenter studies thus providing a framework for the conduct of T&CM. While several studies have reported encouraging results, the quality of the trials precludes their integration into existing standards of practice. We found that for select T&CM supplements, a benefit may be evident. This may have a significant impact in LMICs where access to supportive care medications may be scarce. In these settings, the risks and benefits of T&CM supplements should be weighed prior to their incorporation into care.

The strengths of our systematic review were the clearly defined eligibility criteria, the inclusion of a research librarian for the conduct of a systematic search, the evaluation of evidence from both HIC and LMIC, and the consideration of a quality score for each study. However, there are several limitations to our review, many of which are inherent to the conduct of systematic reviews. Several of the screened studies were not obtained due to inability to contact the authors or inability to locate the published article. It is also plausible that due to limited resources in LMICs, not all clinical studies were submitted for peer review publication. Therefore, we cannot exclude publication bias in our study. We were unable to conduct a formal meta-analysis due to the limited number of studies investigating the same indication and the heterogeneity within the studies that reported on the same outcomes. While we were able to identify areas that appear to be encouraging for future research, it must be recognized that our recommendations evolved from a limited number of clinical studies. Moreover, many of the studies received a low-quality score; thus, our findings are not based upon high-quality clinical trials. Finally, most of the included studies were performed in HIC, thus limiting the generalizability of their findings to the resources available and clinical care delivered to pediatric cancer units in LMICs.

There has been significant scientific effort in advancing the science of T&CM among children with cancer in both HIC and LMIC. Although most studies in this systematic review were of poor quality, a body of literature exists to foster educational and research initiatives. Pediatric cancer units interested in incorporating T&CM into the supportive care needs of children with cancer should consider the existing evidence alongside national policies, barriers in delivering existing care, and indigenous resources to identify the modalities that may be readily integrated into institutional clinical care and whose research findings will have an impact on the quality of care delivered by the institution.

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References

1. American Cancer Society (2015) Global Cancer Facts & Figures, 3rd edn. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-044738.pdf. Accessed 4 Nov 2016
2. Bishop FL, Prescott P, Chan YK, Saville J, von Elm E, Lewith GT (2010) Prevalence of complementary medicine use in pediatric cancer: a systematic review. Pediatrics 125(4):768–776. https://doi.org/10.1542/peds.2009-1775
3. Diorio C, Lam CG, Ladas EJ, Njuguna F, Mbah G, Taromina K, Marjerrison S (2016) Global use of traditional and complementary medicine in childhood cancer: a systematic review. J Glob Oncol. https://doi.org/10.1200/JGO.2016.005587
4. Broom A, Nayar K, Tovey P, Shirali R, Thakur R, Seth T, Chhetri P (2009) Indian cancer patients' use of traditional, complementary and alternative medicine (TCAM) and delays in presentation to hospital. Oman Med J 24(2):99–102. https://doi.org/10.5001/omj.2009.24
5. Handayani K, Sitaresmi MN, Supriyadi E, Widjajanto PH, Susilawati D, Njuguna F, van de Ven PM, Kaspers GJ, Mostert S (2016) Delays in diagnosis and treatment of childhood cancer in Indonesia. Pediatr Blood Cancer 63(12):2189–2196. https://doi.org/10.1002/pbc.26174
6. Hord JD, Rehman W, Hannon P, Anderson-Shaw L, Schmidt ML (2006) Do parents have the right to refuse standard treatment for their child with favorable-prognosis cancer? Ethical and legal concerns. J Clin Oncol Off J Am Soc Clin Oncol 24(34):5454–5456. https://doi.org/10.1200/jco.2006.06.4709
7. Borker A, Chaudhary N (2012) Pattern of refusal to treat and abandonment in a new pediatric oncology unit in southern India. Pediatr Blood Cancer 59(6):1100
8. World Health Organization (2013) World Health Organization traditional medicine strategy: 2014-2023. http://www.who.int/

medicines/publications/traditional/trm_strategy14_23/en/. Accessed 4 Nov 2016
9. Makundi EA, Malebo HM, Mhame P, Kitua AY, Warsame M (2006) Role of traditional healers in the management of severe malaria among children below five years of age: the case of Kilosa and Handeni Districts, Tanzania. Malar J 5:58. https://doi.org/10.1186/1475-2875-5-58
10. World Health Organization (2012) World Health Organization position statement: effectiveness of non-pharmaceutical forms of *Artemisia annua* L. against malaria. http://www.who.int/malaria/publications/atoz/position_statement_herbal_remedy_artemisia_annua_l/en/. Accessed 4 Nov 2016
11. Peltzer K, Friend-du Preez N, Ramlagan S, Fomundam H, Anderson J (2010) Traditional complementary and alternative medicine and antiretroviral treatment adherence among HIV patients in Kwazulu-Natal, South Africa. Afr J Tradit Complement Altern Med 7(2):125–137
12. World Health Organization (1990) Report of the consultation on AIDS and traditional medicine: prospects for involving traditional health practitioners. http://apps.who.int/medicinedocs/en/d/Jh2955e/. Accessed 4 Nov 2016
13. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA (2015) Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev 4:1. https://doi.org/10.1186/2046-4053-4-1
14. The World Bank World Bank Country and Lending Groups. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519. Accessed 4 Nov 2016
15. NIH: National Heart, Lung, and Blood Institute Quality assessment tool for controlled intervention studies. http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/rct. Accessed 4 Nov 2016
16. Hariohm K, Prakash V, Saravankumar J (2015) Quantity and quality of randomized controlled trials published by Indian physiotherapists. Perspect Clin Res 6(2):91–97. https://doi.org/10.4103/2229-3485.154007
17. Gartlehner G, Hansen RA, Reichenpfader U, Kaminski A, Kien C, Strobelberger M, Van Noord M, Thieda P, Thaler K, Gaynes B (2011) Drug class review: second-generation antidepressants: final update 5 report. Oregon Health & Science University, Portland
18. Nozaki T, Kusuzaki K, Takeshita H, Nakamura S, Hashiguchi S, Murata H, Hirasawa Y (2001) Effectiveness of activated vitamin D3 on improving prognosis of osteosarcoma patients. Oncol Rep 8(2):321–324
19. Abu Zaid Z, Shahar S, Jamal AR, Mohd Yusof NA (2012) Fish oil supplementation is beneficial on caloric intake, appetite and mid upper arm muscle circumference in children with leukaemia. Asia Pac J Clin Nutr 21(4):502–510
20. Gong JX, Meng JB, Ma Y (2012) Effects of all-trans retinoic acid and compound huangdai tablet sequential maintenance treatment on the long-term efficacy of acute promyelocytic leukemia patients. Zhongguo Zhong Xi Yi Jie He Za Zhi 32(11):1473–1476
21. Shaban M, Rasoolzadeh N, Mehran A, Moradalizadeh F (2006) Study of two non-pharmacological methods, progressive muscle relaxation and music, on pain relief of cancerous patients. J Fac Nurs Midwifery 12(3):87
22. Tan D, Xie ZZ, Zhong M, Wu D, Liang X, Li W, Qin Q, Tam G (1997) Chinese herbal drugs: sheng-bai-kuai in the treatment of leukopenia caused by chemotherapy. Hunan Yi Ke Da Xue Xue Bao 22(6):547–549
23. Wei YF, Wang SY, Ren LL (2005) Efficacy of shenqi fuzheng injection combined with chemotherapy in treatment of acute leukemia and its effect on T-lymphocyte subsets, serum IFN-gamma, IL-10 and IL-2. Zhongguo Zhong Xi Yi Jie He Za Zhi 25(4):303–306
24. Yan Y (1995) Analysis of therapeutical effectiveness in 35 cases of acute leukemia with therapy of Chinese integrated medicine. Zhongguo Zhong Xi Yi Jie He Za Zhi 15(11):643–645
25. Yang YF, Xu Y, Wu Y (2007) Clinical randomized double-blinded controlled study on Quxie Capsule in reducing post-operational relapse and metastasis of colorectal cancer. Zhongguo Zhong Xi Yi Jie He Za Zhi 27(10):879–882
26. Zhu XY, Zhang XZ, Zhong XY (2010) Effect of shenqi fuzheng injection for hemopoietic and immune function reconstruction in patients with hematologic malignancies undergoing chemotherapy. Zhongguo Zhong Xi Yi Jie He Za Zhi 30(2):205–207
27. Chen QY, Xia JY, Han L (2010) Clinical study on treatment of acute radiation oral mucositis of yin deficiency-induced inner heat syndrome by nourishing yin and clearing heat method. Zhongguo Zhong Xi Yi Jie He Za Zhi 30(7):694–698
28. Fu J, Meng ZQ, Chen Z, Peng HT, Liu LM (2006) Clinical observation on electric stimulation of Yongquan (KI 1) for prevention of nausea and vomiting induced by Cisplatin. Zhongguo Zhen Jiu 26(4):250–252
29. Guo XM, Li JX, Yang XF (1997) Clinical observation on 112 cases with non-Hodgkin's lymphoma treated by Chinese herbs combined with chemotherapy. Zhongguo Zhong Xi Yi Jie He Za Zhi 17(6):325–327
30. Jiang CM, Pang MR, Gong LY (2001) Clinical observation on effect of chemotherapy combined with Chinese medicine in treating advanced tumor patients and on immunologic parameters. Zhongguo Zhong Xi Yi Jie He Za Zhi 21(12):885–887
31. Li HY, Qian LS, Feng SZ (1997) Clinical observation on treatment of complications with Chinese medicine according to syndrome differentiation of post-bone marrow transplantation in 22 patients with leukemia. Zhongguo Zhong Xi Yi Jie He Za Zhi 17(10):581–583
32. RR X, Cao F, Liu ZX (2004) Clinical observation on treatment of acute myelocytic leukemia by supplementing qi, nourishing yin and clearing heat principle. Zhongguo Zhong Xi Yi Jie He Za Zhi 24(5):411–414
33. Wei YF, HL D, Wang SY (2003) Study on efficacy of treatment of acute leukemia by Shengfu injection in combination with chemotherapy and the effect on cellular immunity, serum interleukin-6 and tumor necrosis factor-alpha levels. Zhongguo Zhong Xi Yi Jie He Za Zhi 23(4):258–260
34. Abdulrhman M, Elbarbary NS, Ahmed Amin D, Saeid Ebrahim R (2012) Honey and a mixture of honey, beeswax, and olive oil-propolis extract in treatment of chemotherapy-induced oral mucositis: a randomized controlled pilot study. Pediatr Hematol Oncol 29(3):285–292. https://doi.org/10.3109/08880018.2012.669026
35. Bayram I, Erbey F, Celik N, Nelson JL, Tanyeli A (2009) The use of a protein and energy dense eicosapentaenoic acid containing supplement for malignancy-related weight loss in children. Pediatr Blood Cancer 52(5):571–574. https://doi.org/10.1002/pbc.21852
36. El-Housseiny AA, Saleh SM, El-Masry AA, Allam AA (2007) The effectiveness of vitamin "E" in the treatment of oral mucositis in children receiving chemotherapy. J Clin Pediatr Dent 31(3):167–170
37. Oberbaum M, Yaniv I, Ben-Gal Y, Stein J, Ben-Zvi N, Freedman LS, Branski D (2001) A randomized, controlled clinical trial of the homeopathic medication TRAUMEEL S in the treatment of chemotherapy-induced stomatitis in children undergoing stem cell transplantation. Cancer 92(3):684–690
38. Abdulrhman MA, Hamed AA, Mohamed SA, Hassanen NA (2016) Effect of honey on febrile neutropenia in children with acute lymphoblastic leukemia: a randomized crossover open-labeled study. Complement Ther Med 25:98–103. https://doi.org/10.1016/j.ctim.2016.01.009
39. Miladinia M, Baraz S, Nouri EM, Baesis MG (2015) Effects of slow-stroke back massage on chemotherapy-induced nausea and

vomiting in the pediatrics with acute leukemia: a challenge of controlling symptoms. Int J Pediatr 3(6–2):1145–1152
40. Phipps S, Dunavant M, Gray E, Rai SN (2005) Massage therapy in children undergoing hematopoietic stem cell transplantation: results of a pilot trial. J Cancer Integr Med 3(2):62–70
41. Elbarbary NS, Ismail EA, Farahat RK, El-Hamamsy M (2016) Omega-3 fatty acids as an adjuvant therapy ameliorates methotrexate-induced hepatotoxicity in children and adolescents with acute lymphoblastic leukemia: a randomized placebo-controlled study. Nutrition 32(1):41–47. https://doi.org/10.1016/j.nut.2015.06.010
42. Hagag AA, AbdElaal AM, Elfaragy MS, Hassan SM, Elzamarany EA (2015) Therapeutic value of black seed oil in methotrexate hepatotoxicity in Egyptian children with acute lymphoblastic leukemia. Infect Disord Drug Targets 15(1):64–71
43. Bradfield SM, Sandler E, Geller T, Tamura RN, Krischer JP (2015) Glutamic acid not beneficial for the prevention of vincristine neurotoxicity in children with cancer. Pediatr Blood Cancer 62(6):1004–1010. https://doi.org/10.1002/pbc.25384
44. Mokhtar GM, Shaaban SY, Elbarbary NS, Fayed WA (2010) A trial to assess the efficacy of glutamic acid in prevention of vincristine-induced neurotoxicity in pediatric malignancies: a pilot study. J Pediatr Hematol Oncol 32(8):594–600. https://doi.org/10.1097/MPH.0b013e3181e9038d
45. Wada M, Nagata S, Saito M, Shimizu T, Yamashiro Y, Matsuki T, Asahara T, Nomoto K (2010) Effects of the enteral administration of Bifidobacterium breve on patients undergoing chemotherapy for pediatric malignancies. Support Care Cancer 18(6):751–759. https://doi.org/10.1007/s00520-009-0711-6
46. Rocha KC, Vieira ML, Beltrame RL, Cartum J, Alves SI, Azzalis LA, Junqueira VB, Pereira EC, Fonseca FL (2016) Impact of selenium supplementation in neutropenia and immunoglobulin production in childhood cancer patients. J Med Food 19(6):560–568. https://doi.org/10.1089/jmf.2015.0145
47. Reindl TK, Geilen W, Hartmann R, Wiebelitz KR, Kan G, Wilhelm I, Lugauer S, Behrens C, Weiberlenn T, Hasan C, Gottschling S, Wild-Bergner T, Henze G, Driever PH (2006) Acupuncture against chemotherapy-induced nausea and vomiting in pediatric oncology. Interim results of a multicenter crossover study. Support Care Cancer 14(2):172–176. https://doi.org/10.1007/s00520-005-0846-z
48. Gottschling S, Reindl TK, Meyer S, Berrang J, Henze G, Graeber S, Ong MF, Graf N (2008) Acupuncture to alleviate chemotherapy-induced nausea and vomiting in pediatric oncology—a randomized multicenter crossover pilot trial. Klin Padiatr 220(6):365–370. https://doi.org/10.1055/s-0028-1086039
49. Ndao DH, Ladas EJ, Cheng B, Sands SA, Snyder KT, Garvin JH Jr, Kelly KM (2012) Inhalation aromatherapy in children and adolescents undergoing stem cell infusion: results of a placebo-controlled double-blind trial. Psycho-Oncology 21(3):247–254. https://doi.org/10.1002/pon.1898
50. Mazlum S, Chaharsoughi NT, Banihashem A, Vashani HB (2013) The effect of massage therapy on chemotherapy-induced nausea and vomiting in pediatric cancer. Iran J Nurs Midwifery Res 18(4):280–284
51. Batalha LM, Mota AA (2013) Massage in children with cancer: effectiveness of a protocol. J Pediatr 89(6):595–600. https://doi.org/10.1016/j.jped.2013.03.022
52. Phipps S, Barrera M, Vannatta K, Xiong X, Doyle JJ, Alderfer MA (2010) Complementary therapies for children undergoing stem cell transplantation: report of a multisite trial. Cancer 116(16):3924–3933. https://doi.org/10.1002/cncr.25415
53. Phipps S, Peasant C, Barrera M, Alderfer MA, Huang Q, Vannatta K (2012) Resilience in children undergoing stem cell transplantation: results of a complementary intervention trial. Pediatrics 129(3):e762–e770. https://doi.org/10.1542/peds.2011-1816
54. Post-White J, Fitzgerald M, Savik K, Hooke MC, Hannahan AB, Sencer SF (2009) Massage therapy for children with cancer. J Pediatr Oncol Nurs 26(1):16–28. https://doi.org/10.1177/1043454208323295
55. Haun JN, Graham-Pole J, Shortley B (2009) Children with cancer and blood diseases experience positive physical and psychological effects from massage therapy. Int J Ther Massage Bodyw 2(2):7–14
56. Field T, Cullen C, Diego M, Hernandez-Reif M, Sprinz P, Beebe K, Kissell B, Bango-Sanchez V (2001) Leukemia immune changes following massage therapy. J Bodyw Mov Ther. https://doi.org/10.1054/jbmt.2001.0228
57. Aquino VM, Harvey AR, Garvin JH, Godder KT, Nieder ML, Adams RH, Jackson GB, Sandler ES (2005) A double-blind randomized placebo-controlled study of oral glutamine in the prevention of mucositis in children undergoing hematopoietic stem cell transplantation: a pediatric blood and marrow transplant consortium study. Bone Marrow Transplant 36(7):611–616. https://doi.org/10.1038/sj.bmt.1705084
58. Khurana H, Pandey RK, Saksena AK, Kumar A (2013) An evaluation of vitamin E and pycnogenol in children suffering from oral mucositis during cancer chemotherapy. Oral Dis 19(5):456–464. https://doi.org/10.1111/odi.12024
59. Kokkonen J, Mottonen M, Karttunen TJ, Lanning M (2002) Mucosal pathology of the upper gastrointestinal tract associated with intensive chemotherapy in children: vitamin A supplements do not prevent lesions. Pediatr Hematol Oncol 19(3):181–192. https://doi.org/10.1080/088800102753541332
60. Okur A, Ezgu FS, Tumer L, Cinasal G, Oguz A, Hasanoglu A, Karadeniz C (2006) Effects of oral glutamine supplementation on children with solid tumors receiving chemotherapy. Pediatr Hematol Oncol 23(4):277–285. https://doi.org/10.1080/08880010600628926
61. Sencer SF, Zhou T, Freedman LS, Ives JA, Chen Z, Wall D, Nieder ML, Grupp SA, LC Y, Sahdev I, Jonas WB, Wallace JD, Oberbaum M (2012) Traumeel S in preventing and treating mucositis in young patients undergoing SCT: a report of the Children's Oncology Group. Bone Marrow Transplant 47(11):1409–1414. https://doi.org/10.1038/bmt.2012.30
62. Tomazevic T, Jazbec J (2013) A double blind randomised placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children. Complement Ther Med 21(4):306–312. https://doi.org/10.1016/j.ctim.2013.04.002
63. Uderzo C, Rebora P, Marrocco E, Varotto S, Cichello F, Bonetti M, Maximova N, Zanon D, Fagioli F, Nesi F, Masetti R, Rovelli A, Rondelli R, Valsecchi MG, Cesaro S (2011) Glutamine-enriched nutrition does not reduce mucosal morbidity or complications after stem-cell transplantation for childhood malignancies: a prospective randomized study. Transplantation 91(12):1321–1325. https://doi.org/10.1097/TP.0b013e31821ab959
64. Yildirim ZK, Bidev D, Buyukavci M (2013) Parenteral glutamine supplementation has no effect on chemotherapy-induced toxicity in children with non-Hodgkin lymphoma. J Pediatr Hematol Oncol 35(5):371–376. https://doi.org/10.1097/MPH.0b013e318282daf4
65. Sung L, Tomlinson GA, Greenberg ML, Koren G, Judd P, Ota S, Feldman BM (2007) Serial controlled N-of-1 trials of topical vitamin E as prophylaxis for chemotherapy-induced oral mucositis in paediatric patients. Eur Jo Cancer 43(8):1269–1275. https://doi.org/10.1016/j.ejca.2007.02.001
66. Tacyildiz N, Ozyoruk D, Yavuz G, Unal E, Dincaslan H, Dogu F, Sahin K, Kucuk O (2010) Soy isoflavones ameliorate the adverse effects of chemotherapy in children. Nutr Cancer 62(7):1001–1005. https://doi.org/10.1080/01635581.2010.509841
67. Shi X, Zhu XD, Wang HM (2012) Effects of fuzheng jianpi decoction combined chemotherapy on the quality of life and the survival

time of children with solid tumor. Zhongguo Zhong Xi Yi Jie He Za Zhi 32(9):1175–1179
68. Shi X, Zhu XD, Wang HM (2007) Effect of supporting the healthy energy and strengthening Pi principle of TCM combined with chemotherapy in treating children with solid tumors. Zhongguo Zhong Xi Yi Jie He Za Zhi 27(6):542–545
69. Vieira ML, Fonseca FL, Costa LG, Beltrame RL, Chaves CM, Cartum J, Alves SI, Azzalis LA, Junqueira VB, Pereria EC, Rocha KC (2015) Supplementation with selenium can influence nausea, fatigue, physical, renal, and liver function of children and adolescents with cancer. J Med Food 18(1):109–117. https://doi.org/10.1089/jmf.2014.0030
70. Consolo LZ, Melnikov P, Consolo FZ, Nascimento VA, Pontes JC (2013) Zinc supplementation in children and adolescents with acute leukemia. Eur J Clin Nutr 67(10):1056–1059. https://doi.org/10.1038/ejcn.2013.146
71. Naderi A, Doustan F, Shahabi Nejad A, Dehghani A, Hayatbakhsh Abbasi M (2014) Effects of dietary supplements of pediasure and carnitine on the anthropometric indices in children with acute lymphoblastic leukemia under chemotherapy, in Afzalipour Hospital, Kerman, Iran. J Kerman Univ Med Sci 21(4):332–342
72. Ladas EJ, Kroll DJ, Oberlies NH, Cheng B, Ndao DH, Rheingold SR, Kelly KM (2010) A randomized, controlled, double-blind, pilot study of milk thistle for the treatment of hepatotoxicity in childhood acute lymphoblastic leukemia (ALL). Cancer 116(2):506–513. https://doi.org/10.1002/cncr.24723
73. Garami M, Schuler D, Babosa M, Borgulya G, Hauser P, Muller J, Paksy A, Szabo E, Hidvegi M, Fekete G (2004) Fermented wheat germ extract reduces chemotherapy-induced febrile neutropenia in pediatric cancer patients. J Pediatr Hematol Oncol 26(10):631–635
74. Shi X, Liu Z-M, Zhu X-D (2012) Treatment of vomiting in children patients with solid tumor by hewei zhiou recipe combined ondansetron hydrochloride. Chin J Integr Tradit West Med 32(4):468–470
75. Pillai AK, Sharma KK, Gupta YK, Bakhshi S (2011) Anti-emetic effect of ginger powder versus placebo as an add-on therapy in children and young adults receiving high emetogenic chemotherapy. Pediatr Blood Cancer 56(2):234–238. https://doi.org/10.1002/pbc.22778
76. Diaz PR, Neira LC, Fischer SG, Teresa Torres MC, Milinarsky AT, Giadrosich VR, Arriagada MM, Arinoviche RS, Casanova DM (2008) Effect of 1,25(OH)2-vitamin D on bone mass in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol 30(1):15–19. https://doi.org/10.1097/MPH.0b013e318159a522
77. Dagdemir A, Yildirim H, Aliyazicioglu Y, Kanber Y, Albayrak D, Acar S (2004) Does vitamin A prevent high-dose-methotrexate-induced D-xylose malabsorption in children with cancer? Support Care Cancer 12(4):263–267. https://doi.org/10.1007/s00520-004-0591-8
78. Ladas EJ, Rivas S, Ndao D, Damoulakis D, Bao YY, Cheng B, Kelly KM, Antillon F (2014) Use of traditional and complementary/alternative medicine (TCAM) in children with cancer in Guatemala. Pediatr Blood Cancer 61(4):687–692. https://doi.org/10.1002/pbc.24791
79. Kelly KM, Jacobson JS, Kennedy DD, Braudt SM, Mallick M, Weiner MA (2000) Use of unconventional therapies by children with cancer at an urban medical center. J Pediatr Hematol Oncol 22(5):412–416
80. Hughes D, Ladas E, Rooney D, Kelly K (2008) Massage therapy as a supportive care intervention for children with cancer. Oncol Nurs Forum 35(3):431–442. https://doi.org/10.1188/08.onf.431-442
81. Nahin RL, Boineau R, Khalsa PS, Stussman BJ, Weber WJ (2016) Evidence-based evaluation of complementary health approaches for pain management in the United States. Mayo Clin Proc 91(9):1292–1306. https://doi.org/10.1016/j.mayocp.2016.06.007
82. Vickers AJ, Cronin AM, Maschino AC, Lewith G, MacPherson H, Foster NE, Sherman KJ, Witt CM, Linde K (2012) Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med 172(19):1444–1453. https://doi.org/10.1001/archinternmed.2012.3654
83. Vickers AJ, Linde K (2014) Acupuncture for chronic pain. JAMA 311(9):955–956. https://doi.org/10.1001/jama.2013.285478
84. Berman BM, Langevin HM, Witt CM, Dubner R (2010) Acupuncture for chronic low back pain. N Engl J Med 363(5):454–461. https://doi.org/10.1056/NEJMct0806114
85. Liu F, Han X, Li Y, Yu S (2016) Acupuncture in the treatment of tinnitus: a systematic review and meta-analysis. Eur Archo Otorhinolaryngol 273(2):285–294. https://doi.org/10.1007/s00405-014-3341-7
86. Chiu HY, Hsieh YJ, Tsai PS (2016) Acupuncture to reduce sleep disturbances in perimenopausal and postmenopausal women: a systematic review and meta-analysis. Obstet Gynecol 127(3):507–515. https://doi.org/10.1097/aog.0000000000001268
87. Garcia MK, McQuade J, Haddad R, Patel S, Lee R, Yang P, Palmer JL, Cohen L (2013) Systematic review of acupuncture in cancer care: a synthesis of the evidence. J Clin Oncol Off J Am Soc Clin Oncol 31(7):952–960. https://doi.org/10.1200/jco.2012.43.5818
88. Ladas EJ, Rooney D, Taromina K, Ndao DH, Kelly KM (2010) The safety of acupuncture in children and adolescents with cancer therapy-related thrombocytopenia. Support Care Cancer 18(11):1487–1490. https://doi.org/10.1007/s00520-010-0926-6
89. Jindal V, Ge A, Mansky PJ (2008) Safety and efficacy of acupuncture in children: a review of the evidence. J Pediatr Hematol Oncol 30(6):431–442. https://doi.org/10.1097/MPH.0b013e318165b2cc
90. Chokshi SK, Ladas EJ, Taromina K, McDaniel D, Rooney D, Jin Z, Hsu WC, Kelly KM (2017) Predictors of acupuncture use among children and adolescents with cancer. Pediatr Blood Cancer. https://doi.org/10.1002/pbc.26424