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Nutritional Supplements and Other Complementary Medicines for Infantile Colic: A Systematic Review

Rachel Perry, Katherine Hunt and Edzard Ernst

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Nutritional Supplements and Other Complementary Medicines for Infantile Colic: A Systematic Review

WHAT'S KNOWN ON THIS SUBJECT: Research into complementary and alternative medicines for infantile colic have suggested several therapies that can be beneficial, ranging from supplements to manipulation, sugar solutions, herbal extracts, massage, and reflexology.

WHAT THIS STUDY ADDS: This is the first systematic review of all complementary and alternative medicines and nutritional supplements for the treatment of infantile colic. Encouraging evidence for fennel extract, mixed herbal tea, and sugar solutions were found, but all included trials have limitations.

abstract

FREE

BACKGROUND: Complementary and alternative medicines often are advocated for infantile colic, yet there has been no synthesis of the evidence to inform current practice about their use.

OBJECTIVE: To critically evaluate all randomized clinical trials of nutritional supplements and other complementary and alternative medicines as a treatment for infantile colic.

METHODS: Five electronic databases were searched from their inception to February 2010 to identify all relevant randomized clinical trials of complementary and alternative medicines and supplements for infantile colic. Reference lists of retrieved articles were hand searched. Data were extracted by two independent reviewers, and methodological quality was assessed using the Jadad score and key aspects of the Cochrane risk of bias.

RESULTS: Fifteen randomized clinical trials met the inclusion criteria and were included. Thirteen studies were placebo controlled. Eight were of good methodological quality. Eleven trials indicated a significant result in favor of complementary and alternative medicines. However, none of these randomized clinical trials were without flaws. Independent replications were missing for most modalities.

CONCLUSIONS: Some encouraging results exist for fennel extract, mixed herbal tea, and sugar solutions, although it has to be stressed that all trials have major limitations. Thus, the notion that any form of complementary and alternative medicine is effective for infantile colic currently is not supported from the evidence from the included randomized clinical trials. Additional replications are needed before firm conclusions can be drawn. *Pediatrics* 2011;127:720–733

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KEY WORDS
infantile colic, nutritional supplements, complementary medicine, RCT, systematic review

ABBREVIATIONS
IC—infantile colic
CAM—complementary and alternative medicine
RCT—randomized clinical trial

Rachel Perry, Katherine Hunt, and Edzard Ernst made substantial contributions to the conception and design of this study, acquisition of data, and analysis and interpretation of data; were involved in drafting the article or revising it critically for important intellectual content; and gave final approval of the version to be published.

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Infantile colic (IC) is characterized by excessive and inconsolable crying during the first 4 months of life and often is diagnosed using criteria set out by Wessel et al.[1] It is prevalent (between ~5% and 19% of infants in the United Kingdom)[2] and usually difficult to treat. A paucity of treatment options and dissatisfaction with conventional health care may lead parents to seek out complementary and alternative medicine (CAM) options for their infants.[3] Given that IC can be particularly stressful for new parents and because there are few recommended conventional treatments, CAM use may be high in this population and therefore needs additonal investigation to evaluate the effectiveness of these approaches and treatments. Advice and information regarding the treatment or management of IC is available to parents from a wide range of generally unregulated sources (eg, Web sites) that make claims that are not empirically supported.

The aim of this systematic review is to examine all relevant trials to provide an overview of currently available evidence relating to the effectiveness or efficacy of any form of CAM or nutritional supplement in reducing the symptoms of IC.

METHODS

The following databases were searched from their inception to February 2010; Medline and Embase via the Ovid interface, Cinahl and Amed via the Ebsco interface, and Central via the Cochrane library, using a combination of MeSH and key word terms (see the online Supplemental Information for electronic search strategy). No restrictions were applied regarding language or dates. Reference lists of all full-text articles were hand searched for additional studies. A protocol was produced and adhered to and is available on request from the lead author (Rachel Perry).

Study Selection

All titles and abstracts retrieved from the searches were assessed for eligibility. All articles that appeared to meet the inclusion criteria based on reading the abstract were retrieved in full and independently considered for inclusion by 2 reviewers (Rachel Perry and Katherine Hunt). Disagreements were resolved through discussion with the third author (Edzard Ernst). The following inclusion criteria were predefined:

- Randomized clinical trials (RCTs) of children diagnosed with infantile colic,
- RCTs of any form of CAM, including all supplements and probiotics;
- RCTs with placebo, no treatment, treatment as usual, or waiting lists as control groups; and
- RCTs with the following primary outcomes: improvement from baseline in subjective measures of colic severity (eg, crying diaries, duration, intensity, night wakings, and food diaries); improvement from baseline in parental self-report/observer-completed quality-of-life parameters; improvement from baseline in physiologic parameters; and a reduction from baseline in the need for medication or other treatment of hospitalization or adverse effects or events of treatment.
- Only completed RCTs that met these criteria were included (reports of ongoing trials were excluded). Data from included studies were extracted independently by 2 reviewers (Rachel Perry and Katherine Hunt), using a standardized form with predefined criteria. The proportion of participants achieving clinically significant reductions (defined by authors or using established cut offs) or significant differences in means and medians between groups in any of the above outcomes were reported. Disagreements between reviewers were resolved through discussions with the third author.

Quality Assessment

The methodological quality of all included RCTs was evaluated independently by 2 researchers (Rachel Perry and Katherine Hunt), using the Jadad score.[4] Additional methodological quality data were extracted on the basis of recommendations from the *Cochrane Handbook of Systematic Reviews of Interventions*[5] and the Jadad criteria for clinical trials on pain management.[6]

Analysis

Results of each included study are displayed in Table 1. Between-group analyses of main outcome measures are presented. Secondary analysis was conducted if sufficient data were provided to perform a between-group analysis where the authors had not presented it. A meta-analysis of the primary data was not possible because the RCTs were insufficiently homogeneous.

RESULTS

The literature searches identified 1764 potentially relevant titles and abstracts. Fifteen RCTs with a total of 944 infants met our inclusion criteria (Fig 1). A summary of the main characteristics and results of these RCTs is presented in Table 1 and methodological quality is presented in Table 2. The studies were published between 1991 and 2008, originating from 10 countries. Fourteen studies were in English and 1 was in Danish.[7] Sample sizes ranged from 9 to 175. Trials included infants aged between 0 and 16 weeks.

Eight RCTs[8–14,15] were of good methodological quality and scored 3 or more points on the Jadad scale (Table 2). Seven RCTs[10,15–18,20,21] had a score of 2 or fewer. However, most had

TABLE 1 Results Table

First Author, Date, and Country of Origin	Design	Sample Size Recruited/Randomly Assigned/Analyzed (intervention:control); Diagnosis; Age in days or weeks; Gender; Percentage Breastfed	Intervention Schedule						
			Treatment Group	Control Group	Study Timeline Assessment Schedule	Main Outcome Measures	Main Results (Between-Group Analysis)	Other Outcome Measures	Adverse Events
Supplements									
Akcam, 2006,[8] Turkey	Double blind, placebo-controlled, crossover trial (0 days washout)	30/30/25; Wessel diagnosis; inclusion age range: mean age 9.1 weeks (5.9); 12 male and 13 female; 40	30% glucose solution 1 mL over 15-20 secs for 4 d via dropper when infant continues to cry after attempts to console	Indistinguishable placebo: distilled water for 4 days via dropper when infant continues to cry after attempts to console	4 days in intervention, 4 days in control, no follow-up, assessed at day 4 and day 8	(1) parental assessment rating scale (1–6); (2) clinical exam	(1) 64% versus 48% improvement in intervention condition (McNemar test $P = .031$); (2) not reported	None	No adverse events/effects were noticed
Treem,1991,[9] United States	Double blind, placebo-controlled, crossover trial (1-day washout)	36/33/29 (phase 1) and 27 (phase 2); not Wessel diagnosis; median age 34 days (range: 10–54); 13 male and 14 female; not reported but all fed formula during baseline	Isomil + soy, polysaccharide added; contained 14.1 g total dietry fiber per liter taken for 9 days	Indistinguishable placebo: Isomil; contained only 3.1 g dietry fiber per liter taken for 9 days	6-day baseline measure; 9 days in intervention and 9 days in control; 30- to 35-day follow-up at the end; assessed at the start of baseline, during the intervention, during the control, at the end of the last 9-day period, and at 30–35 days follow-up	(1) Diaries: reporting 15-minute blocks of 24 hours per day	No significant difference in time spent fussing and crying between conditions (Wilcoxon rank-sum tests)	Decision to stay with formula: 18 of 27 selected the intervention formula and 9 of 27 selected the control formula	Not reported
Markestad, 1997,[10] Norway	Double blind, placebo-controlled, crossover trial (0 days washout)	20/19/19; Wessel diagnosis; mean age 7.3 weeks (3.4); 13 male and 6 female; 89	2 mL of 12% sucrose solution over 30–60 seconds via syringe when infant continues to cry after attempts to console	Indistinguishable placebo: distilled water, 2-mL solution over 30–60 seconds via syringe when infant continues to cry after attempts to console	3–4 d in intervention and 6–8 days in control; 3–4 days follow-up (telephone); assessed at the start, after each consultation, and at 3–4 days follow-up	(1) Parental assessment rating scale (0–5); (2) clinical exam	(1) Significant reduction in colic symptoms in sucrose group compared with placebo (McNemar test $P < .01$); (2) not reported	12 of 19 saw specific amelioration from sucrose; 1 of 19 did not improve; 1 of 19 responded specifically to placebo	Not reported
Savino, 2007,[16] Italy	Placebo-controlled, 2-arm trial	90/90 (45:45)/83 (41:42); median age at enrollment: intervention: 31.0 weeks (range: 11–80), control: 31.5 weeks (range 14–74); 44 male and 39 female; 100	*L reuteria* dose of 10^8 in 5 drops of suspension oil 30 min after feeding once per day for 28 days	Placebo: 60 mg per day Simethicone in 15 drops, 2 drops per day after feeding for 28 days	1 day baseline; 28 days intervention; no follow-up; assessed at baseline days 1, 7, 24, 21, and 28	(1) Reduction in daily average crying time (to <3 hours); (2) responders versus nonresponders	(1) Significant reduction in median crying time in intervention group compared with control (difference 95% confidence interval); day 14: intervention 95 (41–170), control 153 (51–231), −58 (−78 to −32); day 28: intervetion 51 (26–105), control 145 (70–191), −94 (−102 to −76); not accounting for baseline median crying time	(2) 95% Responders in probiotic group versus 7% responders in the simethicone group ($P < .001$, χ^2 test for proportions)	No adverse events/effects were noticed

TABLE 1 Continued

First Author, Date, and Country of Origin	Design	Sample Size Recruited/Randomly Assigned/Analyzed (intervention:control); Diagnosis; Age in days or weeks; Gender; Percentage Breastfed	Intervention Schedule						
			Treatment Group	Control Group	Study Timeline Assessment Schedule	Main Outcome Measures	Main Results (Between-Group Analysis)	Other Outcome Measures	Adverse Events
Menthula, 2008,[11] Finland	Double-blind, placebo-controlled, 2-arm trial	27/18/18 (9:9); we were only interested in colicky babies (5:4); Wessel diagnosis; mean age 3 weeks (range: 2–5); 3 male and 6 female	Capsules containing mixture of probiotic bacteria (*L rhamnosus* and *P freudenreichii*) with crystalline cellulose as a filling agent; suspended in water or breast milk 1 time per day for 2 weeks	Indistinguishable; placebo: capsules of microcrystalline cellulose; suspended in water or breast milk 1 time per day for 2 weeks	1 day baseline; 14 days intervention; no follow-up; assessed at 1 week prior to baseline and during week 2	(1) Difference in total crying time; daily diary of sleeping, eating, and crying habits (type and duration)	No significant difference in total crying time between groups (inferential statistics not reported)		No adverse events/effects were reported
Herbal									
Weizman, 1993,[12] Israel	Double-blind, placebo-controlled trial; 4 centers	77/72 (36:36)/68 (33:35); Wessel diagnosis; Age range: 2–8 weeks; 26 male and 42 female; 67	Herbal tea (chamomile, vervain, licorice, fennel, and balm mint) with natural flavors with glucose and hot water. 150-mL dose given at every episode of colic for 7 days (no more than 3 times per day)	Indistinguishable placebo: natural flavors (smell and taste similar); glucose with hot water; 150-mL dose given at every episode of colic for 7 days (no more than 3 times per day)	7 days baseline; 7 days intervention; assessed at baseline, day 7, and day 14	(1) 5-point colic improvement scale; (2) elimination of colic; (3) number of night wakings (needing parental responses)	(1) Day 7: colic improvement score was significantly better in the herbal tea group: 1.7 (0.3) versus the placebo group: 0.7 (0.5), $P < .05$; (Wilcoxon for unpaired samples); (2) more infants in herbal tea group had elimination of colic than the placebo group: 19 of 33 (57%) versus 9 of 35 (26%), $P < .01$ (unpaired t test and χ^2); (3) no significant difference in night wakings		No adverse events/effects were noticed
Alexandrovich, 2003,[13] Russia	Double-blind, placebo-controlled, 2-arm; 2 centers	149/125 (65:60); 121; Wessel diagnosis; age range: 2–12 weeks, mean: intervention 29.7 (8.2) and control 30.5 (6.9); 75	0.1% fennel seed oil emulsion with 0.4% polysorbate in water 5 mL to 20 mL 4 times per day orally before meals (limited to 12 mL/kg per day)	Indistinguishable placebo: 0.4% polysorbate in water 5 mL to 20 mL 4 times per day orally before meals (limited to 12 mL/kg per day)	7 days baseline; 7 days intervention; 7 days posttreatment follow-up; assessed diary entries for 21 days	(1) Pediatric assessment; (2) parental diaries (all episodes of colic night wakings)	There was a significant improvement in colic symptoms in the fennel group compared with control: the use of fennel eliminated colic in 65% of the infants compared with 23.7% in control (Student t test $P < .01$); There was a significant reduction in hours of crying per week in the fennel group compared with control: 8.8 (1.2) versus 12.3 (1.5) (Student t- est $P < .01$); significantly less emulsion consumed per day (mL) in the intervention group 48.9 (6.3) compared with control 52.5 (7.4), $P < .05$		No adverse events/effects were noticed

TABLE 1 Continued

First Author, Date, and Country of Origin	Design	Sample Size Recruited/Randomly Assigned/Analyzed (intervention:control); Diagnosis; Age in days or weeks; Gender; Percentage Breastfed	Intervention Schedule						
			Treatment Group	Control Group	Study Timeline Assessment Schedule	Main Outcome Measures	Main Results (Between-Group Analysis)	Other Outcome Measures	Adverse Events
Savino, 2005,[14] Italy	Double-blind, placebo-controlled, 2-arm trial	93/93 (43:50) 88 (41:47); Wessel diagnosis; age range: 21–60 days, mean intervention 4.2 weeks (1.4) and control 4.4 weeks (1.6); 41 male and 47 female; 100	Colimil: extract of *Matricariae recutita,* (71.10 mg/kg per day), *Foeniculum vulgare* (65.71 mg/kg per day), and *Melissa officinalis* (38.75 mg/kg per day); 2 mL/kg per day 2 times per day between 5 and 8 PM before feeding for 7 consecutive days	Indistinguishable placebo (taste, color, smell, and packaging): containing RO water, fructose, pineapple flavor, citric acid, and sorbate potassium; 2 mL/kg per day 2 times per day between 5 and 8 PM before feeding for 7 consecutive days	7 days baseline; 7 days intervention; 7 days follow-up; assessed at days 1, 7, and 21	(1) Diaries monitoring: crying, when medications administered and side effects; (2) questionnaire about crying for duration of project on day 21; (3) "responders:" crying reduced by 50%	(1) Day 7: significant reduction in mean crying time in the Colimil group 76.9 minutes(23.5) versus 169.9 minutes (23.1) in placebo: (95% confidence interval: −102.89 to −83.11); (2) day 21: significant reduction in mean crying time in the Colimil group 82.1 minutes (19.8) versus placebo 165.3 minutes (20.7) (95% confidence interval: −91.82 to −74.58); not accounting for baseline measures	(3) Responders: 85.4% in the intervention group versus 48.9% in the control group (χ^2 $P < .005$)	Claims there were no adverse events/effects but includes a table of adverse effects (vomiting, sleepiness, restlessness, in appetence, cutaneous reactions, and constipation)
Massage									
Huhtala, 2000,[17]•••	No blinding; placebo-controlled, 2-arm trial	85/60/58 (28:30); Wessel diagnosis; age range: 23–48 days, mean intervention 39.5 (7.2) and control 37.3 (7.7); 32 male and 36 female; 100	Infant massage: 3 times per day (2 time per day whole body when baby is calm, 1 time belly massage when colicky); mothers trained by nurses and brochure	Placebo: crib vibrator (previously ineffective in colic study) 3 times per day for 25 min during colic or in advance of usual colicky episodes	1 week baseline; 3 weeks intervention; assessed at baseline, 1 week (telephone), and during the third-week visit	(1) Weekly diaries: 1 week prior to entry and for the 3 weeks of intervention; (2) rating scale of colic symptoms; (3) rating scale of effect of intervention	At 4 weeks: (1) no significant difference in colicky crying (48% in massage versus 47% in vibrator), $P = .87$; At 3 weeks: (2) bo significant difference in colicky symptoms (64% in massage versus 52% in vibrator), $P = .24$; (3) no significant difference in parental evaluation of effectiveness of intervention between groups	93% in both groups reported a decrease in colic symptoms, yet 21% in massage and 30% using the crib vibrator had no given effect of intervention	Not reported
Reflexology									
Bennedbeak, 2001,[7] Denmark	2 placebo-controlled interventions versus TAU; 3 arms	63/30/28 (8:10:10); No Wessel diagnosis; aged 1–3 months; gender not reported; breastfeeding not reported	Group B (targeted reflexology): 20-min sessions (4 days) over a 2-week period	Indistinguishable placebo: Group A (nontargeted reflexology): 20-min sessions (4 days) over a 2-week period; Group C: control (TAU)	2 days baseline; 14 days intervention; assessed at baseline and final Q	(1) Questionnaire; (2) journal 3 times per day: crying, bowel habits, and sleep patterns; drop-out form	No significant difference between Groups A and B; control group: none were cured; Groups A and B: half the sample was cured; Group B: did significantly better than Group C in terms of reduction in crying hours; all data not presented		Not reported

TABLE 1 Continued

First Author, Date, and Country of Origin	Design	Sample Size Recruited/Randomly Assigned/Analyzed (intervention:control); Diagnosis; Age in days or weeks; Gender; Percentage Breastfed	Intervention Schedule						
			Treatment Group	Control Group	Study Timeline Assessment Schedule	Main Outcome Measures	Main Results (Between-Group Analysis)	Other Outcome Measures	Adverse Events
Manipulation									
Wiberg, 1999,[18] Denmark	No blinding; prospective RCT; placebo controlled, 2-arm, open trial	57/50 (25:25)/45 analyzed (25:20), dropped further to 41; no Wessel diagnosis; inclusion age range: 2–10 weeks, mean intervention 4.9 (0.5) and control 5.9 (0.7); 25 male and 20 female; breastfeeding not reported	Chiropractic manipulation (3–5 treatments) over 12–15 days plus counseling	Placebo: Dimethicone daily for 12–15 days plus counseling	4 days baseline; 12–15 days treatment; assessed at end of weeks 1 and 2	(1) Colic diary: (a) periods of awake/sleep/crying, (b) bowel movements, (c) feeding patterns, (main outcome percentage change); (2) structured diagnostic interview (IC behavior profile) measuring parents subjective evaluation of severity	Changes in colic (hours per day crying); days 4–7: significant reduction in crying in the Dimethicine group −1.0 (0.6) versus manipulation −2.4 (0.4), $P = .04$ (change score unpaired t test); days 8–11: significant reduction crying time in the Dimethicone group −1.0 (0.4) versus manipulation −2.7 (0.3), $P = .004$ change score unpaired t test); after day 12 missing records precluded analysis		Not directly reported but worsening of colic symptoms in control group
Mercer, 1999,[19] New Zealand	Single-blind, placebo-controlled	30 infants with colic (15:15); diagnosis not reported; age range: 0–8 weeks; gender not reported; breastfeeding not reported	Chiropractic spinal manipulation, maximum of 6 treatments over 2 weeks	Placebo: nonfunctional, detuned ultrasound machine, 6 treatments over 2 weeks	Baseline; 2 weeks intervention; 1 month follow-up; assessed at baseline, at each consultation, and at 1 month follow-up	Parental questionnaires	Mann-Whitney U test: 93% complete resolution of symptoms in spinal manipulation group (plus no reoccurrence of colic at 1 month)		Not reported
Olafsdottir, 2001,[15] Norway	Double-blind, placebo-controlled, 2-arm trial	100/91/86 (46:40); Wessel diagnosis; age range: 3–9 weeks; 47 male and 39 female; breastfeeding not reported	Chiropractic manipulation for 10 min 3 times in 8 days	Placebo: held by nurse for 10 min 3 times in 8 days	2 days baseline; 8 days intervention; 14 days follow-up; assessed with a clinical exam at each visit, every 2–5 days of the intervention, and at 8–14 days follow-up (telephone)	(1) Observation scale (1–5); (2) crying diaries; (3) clinical assessment	(1) Main outcome at day 8: intention-to-treat sample: no significant difference between groups on parent report (Mann-Whitney U test $P = .861$, Fischer's test $P = .656$); (2) no significant difference in crying (diaries), intervention (69.9%) versus control (60.0%) improved but no significant difference between groups based on the t test ($P = .982$); no follow-up analysis presented		Not reported

TABLE 1 Continued

First Author, Date, and Country of Origin	Design	Sample Size	Intervention Schedule						
		Recruited/Randomly Assigned/Analyzed (intervention:control); Diagnosis; Age in days or weeks; Gender; Percentage Breastfed	Treatment Group	Control Group	Study Timeline Assessment Schedule	Main Outcome Measures	Main Results (Between-Group Analysis)	Other Outcome Measures	Adverse Events
Hayden, 2006;[20] United Kingdom	No blinding, open-controlled, 2-arm trial	44/28 (14:14) dropped to 26 (14:12); No Wessel diagnosis; mean age: intervention 46.4 days (5.4) and control 44.5 days (5.0) (range: 10–83); 22 male and 6 female; 61	Cranial osteopathy (individualized) 1 time per week for 4 weeks; received cranial osteopathic treatment until palpable release of tensions and dysfunction achieved; first session was 1 hour then 4 30min sessions	No treatment	Baseline; 4 weeks intervention; no follow-up; assessed at the clinical exam at baseline and 1, 2, 3, and 4 weeks (plus daily diary)	(1) Diaries: number of hours per day spent colicky crying and number of hours per day spent sleeping; (2) questionnaire about birth details, sleeping, and feeding patterns	Between weeks 1 and 4: (1) a significant reduction in mean crying time in the treated group compared with the nontreated group: 1.0 hours per day (95% confidence interval: 0.14–2.19) (2-sample t test $P < .02$); (2) a significant increase in mean sleeping time in the treated group compared with the nontreated group: 1.17 hours per day (95% confidence interval: 0.29–2.27) (2-sample t test $P < .05$)	All infants in the treatment group showed improvement, but only 2 of 14 in the control group; no inferential statistics were reported	No adverse events were noticed
Massage, Fennel Tea, and Sucrose Solution									
Arikan, 2008[21] Turkey	No blinding, 5-arm open trial	187/175 (35:35:35:35:35:35); $N = 140$; Wessel diagnosis; mean age: massage group 2.29 weeks (.75), sucrose group 2.24 weeks (0.69), herbal tea group 2.24 weeks (0.69), control group 2.28 weeks (0.61); 97 male and 78 female; 100	(1) Infant massage (CSM) 2 times per day for 25 min during colic symptoms; (2) sucrose supplement: 2 mL of 12% sucrose solution 2 times per day between 5 PM and 8 PM; (3) herbal tea (fennel): 35 mL 3 times per day (maximum 150 mL)	No treatment	1 week baseline; 1 week intervention; no follow-up; assessed at 1 week baseline (diary) and 1 week intervention (daily diary)	(1) Baseline questionnaire: (behavior, temperament, sleeping, eating, and history of colic); (2) crying diary	Significant reduction in all treatment groups compared with the control group (using the Dunnet t multiple-comparison test); massage versus control: 0.88 (0.28) ($P < .01$); sucrose versus control: 1.68 (0.28) ($P < .001$); herbal tea versus control: 1.82 (0.28) ($P < .001$)		Not reported: mentioned in discussion but not type or percentage

[a] Data not included from the hydrolyzed formula group because it is not CAM therapy.

methodological flaws that limited the conclusiveness of their findings. Only 4 trials[9,11,15,21] used intention-to-treat analyses, and 3[9,11,21] were the result of having no dropouts. The majority of trials did not conduct power calculations; thus, the role of chance was not quantified, reducing the reliability of the results. For clarity, the results of the 15 trials are described under specific treatment headings. Variation in the information given for each trial is a result of differences in the availability of the data.

Manipulation Studies

Four studies of manipulation were reviewed. Three studies show a significant effect from intervention treatment. Wiberg et al[18] found a significantly greater reduction in mean hours of crying in manipulation compared with dimethicone at days 4 to 7 days ($P < .04$) and days 8 to 11 ($P < .004$) (after day 12 the number of missing records preclude analysis). Data for analysis only were available for 41 of 50 subjects. Interestingly, all post-baseline dropouts ($n = 4$) were in the control group and were attributed to worsening colic symptoms. Because an intention-to-treat analysis was not conducted, there may be a bias in favor of the spinal-manipulation group because results from the worsened cases were not included in the analysis, thus somewhat undermining the significant findings. Because of a variation in the treatment type and duration, the therapeutic time was not equivalent between groups, which is an additional source of bias.

Mercer and Nook[19] reported a complete resolution of symptoms in 93% of infants and no reoccurrence at the 1-month follow-up, which was significant compared with the placebo group. However, the results from the placebo group and statistical test are not reported. No details were given

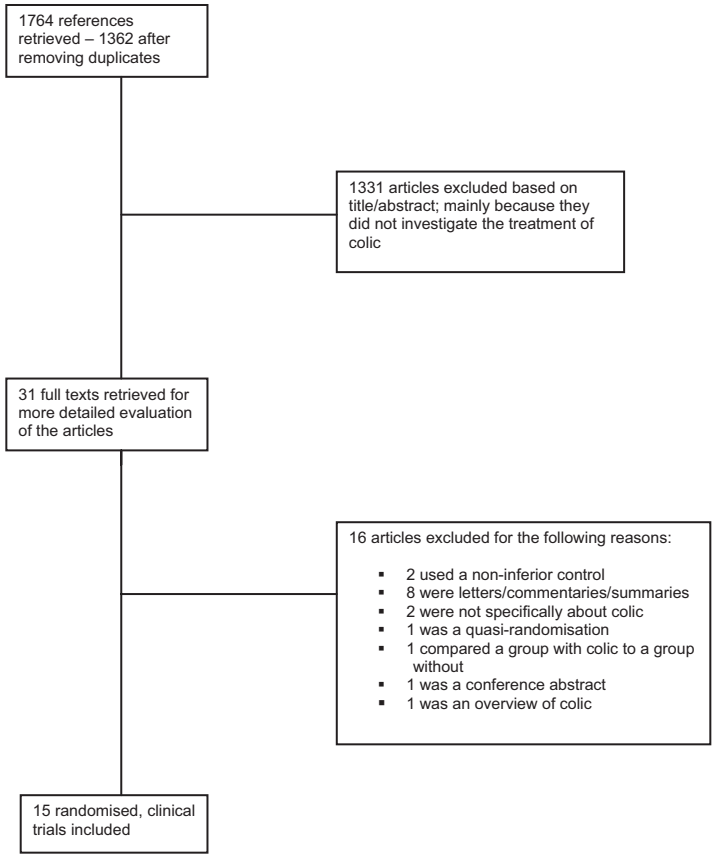

FIGURE 1
Flowchart showing the process for the inclusion of randomized controlled trials.

on the randomization procedure or whether treatment allocation was concealed, and it was not clear whether groups were similar at baseline on prognostic indicators. Although the study is described as a single-blind study, it is not explicitly stated that parents were actually blinded to treatment. Numbers of dropouts and reasons for dropping out were not reported, and it was unclear whether there was a difference in the number of actual sessions between the groups because it just states up to 6 sessions. In general, this trial was of poor methodological quality (Jadad 1), was very briefly outlined, and had too much missing information to enable replication.

Hayden and Mullinger[20] conducted a pragmatic trial looking at the impact of cranial osteopathy compared with no treatment for colic. Results indicated a significant reduction in crying ($P < .02$) and a significantly greater increase in sleeping time ($P < .05$) in the intervention group compared with the control group. The control group received no treatment, just therapeutic time, thus the parents were not blinded. Given that parents reported on treatment effectiveness, blinding to the results is essential to reduce the effect of demand characteristics or the Hawthorne effect. Failure to blind parents to the results may therefore have increased the risk of bias and reduced the validity and reliability of the results.

A final study of chiropractic treatment[15] showed no differences in outcome according to parent's reports or hours of crying recorded in the diaries in both the intention-to-treat and per-protocol analyses. All parties were blinded to the results except the chiropractor. The parents/outcome assessors were unlikely to be aware of treatment conditions because a nurse took the infant to a closed room where they were either manipulated by a chiropractor or held by a nurse (controlling for any nonspecific effects [eg, touch by a stranger]). However, it does leave the question of whether the nurse would unconsciously transmit the group allocation. Overall, this is the most reliable study on manipulation.

Herbal Studies

Three studies on herbal supplements were reviewed, and all 3 reported significant results. One well-conducted study[13] (Jaded 5) reported a significant improvement in colic symptoms in infants given fennel extract compared with placebo ($P < .01$). In another trial,[12] herbal tea (containing chamomile, vervain, licorice, fennel, and balm-mint) significantly improved the colic score ($P < .05$) and resulted in a greater elimination of colic symptoms ($P < .01$) than placebo. However, although both these trials used large samples ($n = 125$ and $n = 72$, respectively), neither reported a power calculation nor conducted intention-to-treat analyses, which somewhat reduces the robustness of the findings.

Savino et al[14] compared Colimil (a herbal formula containing fennel, lemon balm, and German chamomile) to an indistinguishable placebo. There was a significant difference in crying times per day at the end of the trial and at the 15-day follow-up, with a greater reduction in crying in the Colimil group compared with the control group. The statistical methodology stated that an analysis of variance was used, yet independent *t* tests were reported, therefore not accounting for baseline crying time (although this might be because no between-group differences

TABLE 2 Methodological Quality of Trials

First Author, Date	Was the Treatment Allocation Randomly Assigned?	Was the Randomization Procedure Described and Was It Appropriate?	Was the Treatment Allocation Concealed?	Were Groups Similar At Baseline on Prognostic Indicators?	Who Was Blinded?	Was the Trial Described As Double Blind?	Was the Method of Blinding Described and Appropriate?	Was the Number of Withdrawals/ Dropouts in Each Group Mentioned?	In Addition, Were Reasons Given for Each Group?	Was Analysis Conducted on the Intent-to-Treat Group?	Was an A Priori Power Calculation Described?	Were Comorbidities Avoided/Controlled For?	Was the Therapeutic Time Equivalent Between Groups?	Jadad Score, Maximum Score = 5	Where Relevant, How Many Items in Section 4 of the Herbal-Specific CONSORT Statement Were Described Fully and Partly (F/P)?
Supplements															
Akcam, 2006)[7]	Yes	Not described	Unclear[a]	Yes[b]	Parents/clinical observers blinded; parents blinded	Yes	Yes[c] (indistinguishable placebo)	Not by group/ yes by group	Not by group/ yes by group	No	No	Yes (excluded at baseline)	Yes	3	
Treem (1991)[8]	Yes	Not described	Not reported	Yes[b]	Outcome assessor not reported; parents/ clinical observers blinded	Yes	Yes (indistinguishable placebo)	No dropouts	NA	No	Yes	Yes (excluded at baseline)	Yes	4	
Markestad (1997)[9]	Yes	Not described	Unclear[a]	Yes[b]	Parents not blinded; pediatrician not reported	Yes	Yes[c] (indistinguishable placebo)	Yes by group/no drop outs	Yes by group	Yes[e]	No	Yes (excluded at baseline)	Yes	4	
Savino (2007)[10]	Yes	Yes	Unclear	Yes	Parents blinded; assessors not reported	No	—		NA	No	Yes	Yes (excluded at baseline)	No[f]	2	
Menthula (2008)[11]	Yes	Not described	Not reported	No		Yes	Yes (indistinguishable placebo)			Yes[e]	No		Yes	3	
Herbal Extracts															
Weizman (1993)[12]	Yes	Not described	Not reported[d]	Yes	Parents blinded; outcome assessor not reported; parents, lab technician	Yes	Yes (indistinguishable placebo)	Yes by group	Yes by group	No	No	Yes (excluded at baseline)	Yes	4	2/3
Alexandrovich (2003)[13]	Yes	Yes	Yes	Yes	Pediatric assessor/ research analyst blinded; parents/ pediatrician blinded	Yes	Yes (indistinguishable placebo)	Yes by group	Yes by group	No	No	Yes (excluded at baseline)	Yes	5	3/2
Savino (2005)[14]	Yes	Not described	Not reported	Yes		Yes	Yes (indistinguishable placebo)			No	No		Yes	3	3/3
Massage															
Huhtula (2000)[15]	Yes	Not described	Not reported	No	Parents not blinded; pediatrician and nurse not reported	No	—	Yes by group	Yes by group	No	No (post hoc)	Yes (excluded at baseline)	Unclear[g]	2	
Reflexology															
Bennedbaek (2001)[16]	Yes	Yes	Not reported	Not reported	Parents blinded between groups A and B but not between group C; Outcome assessor not reported	No	No	Yes by group	Yes by group	Unclear[h]	Unclear[h]	Yes (excluded at baseline)	Yes between Groups A and B but not C	2	

TABLE 2 Continued

First Author, Date	Was the Treatment Allocation Randomly Assigned?	Was the Randomization Procedure Described and Was It Appropriate?	Was the Treatment Allocation Concealed?	Were Groups Similar At Baseline on Prognostic Indicators?	Who Was Blinded?	Was the Trial Described As Double Blind?	Was the Method of Blinding Described and Appropriate?	Was the Number of Withdrawals/ Dropouts in Each Group Mentioned?	In Addition, Were Reasons Given for Each Group?	Was Analysis Conducted on the Intent-to-Treat Group?	Was an A Priori Power Calculation Described?	Were Comorbidities Avoided/Controlled For?	Was the Therapeutic Time Equivalent Between Groups?	Jadad Score, Maximum Score = 5	Where Relevant, How Many Items in Section 4 of the Herbal-Specific CONSORT Statement Were Described Fully and Partly (F/P)?
Manipulation															
Wiberg (1999)[17]	Yes	Not described in enough detail; not described	Not reported	No	Parent not blinded; nurse assessor blinded	No (single blind)	—	Yes by group/No	Yes by group/No	No	No	Yes (excluded at baseline)/not reported	No	1	
Mercer (1999)[18]	Yes	Not described	Not reported	Not reported	not explicit that parents were blinded; parents/ pediatrician/ researcher all blinded	No (single blind)	—	Not by group	Not by group	No	No	Yes	Unclear[i]	1	
Olafsdottir (2001)[19]	Yes	Yes	Unclear[d]	Yes	Chiropractor and nurse not blinded; no one (open trial)	No[j]	Yes	Yes by group	Yes by group	Yes	No	(excluded at baseline)	Yes	3	
Hayden (2006)[20]	Yes		No	Yes		No	—			No	No	Yes (excluded at baseline)	Yes	2	
Massage, Fennel Tea, and Sucrose Solution															
Arikan (2008)[21]	Yes	Not described[k]	Not reported	Not clear[l]	Parents not blinded; pediatrician and researcher not reported	No	—	No dropouts	NA	Yes	No	Yes (excluded at baseline)	No	1	1/1

[a] Used sealed envelopes but did not state if they were opaque.
[b] Same participants (crossover trial).
[c] Pharmacist was the only 1 aware of coding.
[d] Pharmacy controlled.
[e] As a result of no dropouts.
[f] Therapeutic time was difficult to achieve because of the different dosage requirements of the 2 treatments.
[g] A slight difference in the number of hours of treatment, but no test of difference was carried out.
[h] Unclear from translation.
[i] Up to 6 sessions.
[j] Not described as double blind but parent and outcome assessor were both blinded.
[k] Randomization of the breast-fed group only included here.
[l] Colic severity was not mentioned.

were found in crying time at baseline). Savino et al also reported a significant reduction in crying time between "responders" and "nonresponders" (85.4% in the Colimil group vs 48.9% in the control group; $P < .005$). Responders were defined as infants who had a 50% reduction in crying time at the end of treatment; however, this was a subgroup of the original sample, so sample sizes were small and there is no control over bias in these cases. There also is some confusion regarding adverse effects; the authors reported no adverse effects yet they present a table of side effects (eg, vomiting, sleepiness, constipation, loss of appetite, and cutaneous reactions).

Glucose and Sucrose Studies

Five studies on supplements were found. Akçam and Yilmaz[8] and Markestad[10] tested glucose and sucrose supplementation, respectively. Akçam and Yilmaz[8] replicated Markestad's[10] design but investigated glucose rather than sucrose, describing it as a safer treatment.[8] Both found significant effects of the intervention compared with placebo (McNemar test: $P = .031$ and $P < .01$). However, the McNemar matched-pairs test (which is performed on dichotomous data) was used on continuous variables and an explanation of cut offs used to dichotomize the variables was not provided in either trial. Given that a test designed for continuous data would have been more appropriate for both these trials, there is the possibility that selective reporting took place. Markestad[10] had higher methodological quality than the other trials (Jadad 4), but a lack of washout between the conditions made it impossible to ascertain which treatment induced the effect in 5 infants. Despite using an identical placebo in both trials, and despite the parents claiming that they did not taste the difference between the solutions, it still was possible to do so, which could have then affected the subjective rating of colic severity.

Probiotics Studies

Savino et al[16] found a significant reduction in median crying time in the probiotic condition compared with the control group at day 7 ($P < .005$) and up to day 28 ($P < .001$). Although this analysis did not account for baseline interactions, mean crying time was exactly the same in both groups at baseline. Using the same criteria to define "response to treatment" used in the other Savino et al trial,[14] the authors reported that 95% of infants in the probiotic group responded to treatment compared with only 7% in the simethicone group. This is pertinent given that simethicone is considered the best available and most commonly prescribed treatment for colic, although it previously has been shown to be no more effective than the placebo.[22,23] Despite some poor reporting of results, and the fact that the trial could not be conducted in a blinded manner because of the different dosage and administration requirements of the 2 solutions, this was the only trial to control for the confounding effect of the mother's diet. Moreover, this was 1 of only 2 trials that reported a power calculation[9,11]; but given that the authors recruited beyond the required sample size (doubling the required numbers in each group), it may be fair to assume that a post hoc calculation was conducted.

Treem et al's[9] results indicate that although a soy-enriched formula did not significantly improve the effects of colic, the parents were happier (67%) using the intervention formula than the control formula (33%). Unfortunately, only a 1-day washout period was used, which may have impacted on the results. Menthula et al's[11] study used both colicky and noncolicky infants randomly assigned to probiotic capsules or an indistinguishable placebo, and although we were only interested in the colicky sample, at times it was difficult to separate the analyses. Colicky cry decreased more in the placebo group yet was more marked at baseline (significance level not reported). The sample size was very small ($n = 9$); therefore, it was difficult to extrapolate from these findings, but the results showed no significant difference in reduction of total crying times between groups. In both these trials,[9,12] the statistical test was not reported.

Massage Studies

In 1 study of massage,[15] massage therapy was compared with a mechanical crib vibrator so the therapeutic effects of touch were not controlled for (although the parents were led to believe that the crib vibrator was of equal value to massage). However, the crib vibrator group had significantly more colicky crying at baseline ($P = .021$), which may have impacted on the results. Results showed no significant differences between groups in terms of a decrease in crying or colicky symptoms. Interestingly, 93% of parents in both groups reported a decrease in colic symptoms over the duration of the trial, but this is contradicted by the fact that 21% of the massage group and 30% of the crib-vibrator group reported no given effect of treatment, which may suggest that a reduction in colic severity was associated with the natural course of the condition rather than either intervention.

Reflexology Studies

The reflexology trial[7] used less stringent IC diagnostic entry criteria than the other trials but examined and removed infants with other medical problems before they were randomly assigned. There were 2 reflexology groups (nonspecific reflexology [A

group] and colic-specific reflexology [B group]) versus a treatment-as-usual control (C group). The nonspecific reflexology did not target the areas of the feet considered to be therapeutic for colic, whereas the colic-specific reflexology targeted the spine, digestion, colon, spleen, lungs urinary tract, solar plexus, and endocrine points. The findings show a significant difference between group B and the control but no significant difference between the 2 treatment groups (A and B). This implies that targeted reflexology is no better than nontargeted reflexology in the treatment of IC; any improvement in colic found in the 2 treatment groups compared with the control group may have more to do with the therapeutic effect of touch than the actual therapy itself. However, with a small sample size ($n = 28$) and no power calculation, it is difficult to establish the true magnitude of the results, particularly given the absence of inferential statistical analyses.

Massage, Fennel Tea, and Sucrose Solution Studies

Another study[21] investigated the effectiveness of four different interventions versus control. Because we were only interested in the 3 CAM therapies (massage, sucrose solution, and fennel tea), the results from the hydrolyzed formula group are not reported here. Results indicated a significant difference between all groups and the control group (massage: $P < .01$; sucrose solution and [fennel] tea: $P < .001$). A large sample was recruited to these 4 groups ($n = 140$), although no power calculation was reported. For consistency, the same nurse and pediatrician were involved in each intervention and replicated methodologies and treatment protocols from previous studies, where possible. Unfortunately, the treatment duration and follow-up period were short (reducing the likelihood of identifying side effects), and there was no matching of therapeutic time for the control group. However, this was the only trial that accounted for the mother's anxiety levels, excluding those with high anxiety before entry.

DISCUSSION

Our review included 15 RCTs of 5 different CAM modalities. Most studies were flawed, reducing the robustness of their findings. The most promising results emerged for fennel extract, herbal tea (containing chamomile, vervain, licorice, fennel, and balm mint), and sucrose and glucose solutions. However, independent replications are missing for all tea extracts except fennel, and there has been no replication of the glucose solution. Thus, only fennel extraction and sucrose solution are supported by positive evidence from more than 1 RCT.

The majority of the included trials in this review eschewed safety issues by not mentioning adverse effects and not providing reasons for subjects dropping out. This is a frequent phenomenon in CAM research, and there is a common misconception that natural means safe.[24] Researchers investigating botanical products should comply with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for the reporting of herbal products.[25] None of the included trials of herbal products[12–14,21] provided information that met more than 6 of 15 CONSORT statement criteria regarding the extraction and preparation of herbs.[25] Future trials also would benefit from adopting good trial design and stringent reporting to enable replication. This would include adopting a randomized design with allocation concealment, being triple blind (if possible), and having indistinguishable placebos. All withdrawals, dropouts, and adverse events should be fully reported, giving number and reason by group. Intention-to-treat analyses and a priori power calculations should be conducted. Given that funding for CAM research is difficult to obtain and our review did not identify convincing evidence for the use of manual therapies (chiropractic, massage) and probiotics, additional research should focus on the treatments that offer more robust evidence.

IC is a condition that is far from easy to treat. Current conventional treatments fall into 1 of the following 4 categories: dietary, physical, behavioral, and pharmacological. With little evidence to favor the first 3 approaches, there is some evidence that the drug dicyclomine hydrochloride can be effective, although its safety came into question after reports of severe side effects occurring in ~5% of infants,[26] and in some extreme cases it has been linked to infant death.[27]

The difficulty in finding an effective treatment is related to our lack of understanding of IC. Its pathophysiology is unclear; food allergies, formula intolerance, immaturity of gastrointestinal tract, excessive gas formation, or intestinal cramping have all been suggested as possible etiologies.[13] Arguably, any rational treatment should be directed at the mechanisms of the disease itself.

Indeed, animal studies[28] have demonstrated that fennel may have an intestinal antispasmodic effect and might increase small-intestine motility. Some researchers have claimed that volatile oil extracted from fennel is particularly effective in relieving colic symptoms.[13] The reason for using sucrose in IC is based on research demonstrating an analgesic effect in newborn infants undergoing heel-prick tests.[29,30] The mechanism by which this occurs is unknown, although it has been postulated that its sweetness has the analgesic effect or that it induces a physiologic effect to the structure of

the gut wall.[9] Additional research into these mechanisms is required.

The remaining CAM modalities in this trial have questionable biological plausibility for IC, and it should be acknowledged that there remains a deficit in the evidence base for many CAM therapies. However, the nonspecific effects (eg, placebo, therapeutic effects of time, attention, touch) of many CAM therapies generally are poorly understood but are likely to play a role.

The self-limiting nature of IC means that assessments of the effectiveness of treatments are best conducted in the form of RCTs. This is not to suggest that symptoms should not be addressed. Without symptom relief, IC can lead to unnecessary medical intervention (including hospitalization), can affect the parent–child bonding process, and, in rare cases, lead to child abuse.[31] Future research should perhaps be directed at better understanding IC so that effective treatments can be developed.

This review has several limitations. Although the search strategy was thorough, some clinical trials may not have been identified. However, our systematic and detailed search strategy should have assisted in identifying all trials and in reducing bias. Nevertheless, publication bias is a problem in all medical research,[32] and it is particularly problematic in alternative medicine.[33,34] Other limitations are the paucity and often poor quality of the primary studies. Collectively, these limitations render our review less than conclusive.

CONCLUSIONS

Few RCTs of CAM for IC are available, and many have methodological problems that limit the potential to draw reliable conclusions about the efficacy of CAM and supplements for IC. Although some encouraging results exist for fennel extract, mixed herbal tea, and sugar solutions, design flaws and the absence of independent replications preclude practice recommendations. The evidence for probiotic supplements and manual therapies does not indicate an effect. Thus, the notion that any form of CAM is effective for infantile colic is currently not supported from the evidence from the included RCTs. Additional research into this prevalent, and often difficult to treat, condition seems warranted.

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ALARM FATIGUE: *A few days ago, I was seeing a hospitalized patient of mine. While I was talking to her and her mother, the oxygen saturation and cardiopulmonary monitoring alarms went off several times. As she was not in distress and acyanotic, I eventually silenced the alarms so I could continue my interview and examination. It would appear that I am not alone in ignoring alarms. Fortunately, however, my patient did not suffer any ill consequences because of my actions. According to an article in* The Boston Globe *(February 13, 2011: Lifestyle), patient alarms often go unheeded. Part of the problem is that the nursing staff may be experiencing alarm fatigue. Patients are attached to many different monitoring devices which sound all kinds of alarms, from quieter low level alerts to louder and more piercing critical illness alerts. Nurses are constantly addressing one alarm after another. In one 15 bed hospital unit, the staff documented 942 alarms a day. Over time, nurses can become desensitized. Moreover, most alarms are false. According to the article, in one hospital emergency room, 99.4 percent of alarms were false and for patients with chest pain, less than 1 percent of alarms necessitated a change in patient care. In another study in an intensive care unit, 43 percent of crisis alarms were false. Device manufacturers have an interest in making sure the monitors are sensitive rather than specific to avoid missing a potential devastating problem. With alarms sometimes becoming just background noise, bad outcomes are bound to occur. An investigation by* The Boston Globe *revealed that between 2005 and 2010, more than 200 deaths were linked to alarms. Most of the time, the problem was not that the alarm did not go off but that the alarm had been disabled, silenced, or ignored. There does not seem to be an easy solution to this problem. So while I was a bit frustrated by intrusiveness of the incorrect alarms while talking with my patient, I repositioned the pulse oximeter probe as best I could, turned the alarm back on, and before leaving, made sure I talked to my patient's nurse.*

Noted by WVR, MD

Nutritional Supplements and Other Complementary Medicines for Infantile Colic: A Systematic Review

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