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Review Article

Efficacy of Aromatherapy on Children: A Systematic Review with Meta-Analysis

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Background. Aromatherapy is one of the most commonly practiced complementary therapies by nurses, identified as central to holistic nursing care and in line with nursing theoretical foundations. Although it is also a widely used intervention in children, studies that have made a quantitative synthesis of its effect on this population are lacking in the literature.

Objective. To assess the effectiveness of aromatherapy in reducing procedural pain, anxiety, stress-related physiological responses, and in improving sleep duration among pediatric patients undergoing diagnostic or therapeutic procedures.

Methods. Studies were searched from biomedical databases, trial registries, web resources, and refereed journals. The risk of bias of included studies was assessed with RoB 2 and ROBINS-I, and the overall effect size of the intervention was calculated by creating random-effects meta-analyses graphically represented by forest plots. The summary of results was illustrated with a table in accordance with the GRADE method.

Results. Thirty-three studies with generally high risk of bias were included (N = 2650, mean age: 1.8 days-12.3 years, males: 33%-75%). Aromatherapy appears to have a positive and large effect on pain [SMD = -1.12 (95% CI: -1.60, -0.65), N = 1794, 27 comparisons, 22 studies], anxiety [SMD = -1.08 (95% CI: -1.52, -0.64), N = 856, 15 comparisons, 9 studies] and sleep duration [SMD = -0.95 (95% CI: -1.94, 0.03), N = 330, 4 studies]; in addition, it also appears effective on physiological signs of stress. The certainty/quality of evidence is very low.

Conclusions. Due to the very low certainty/quality of evidence, at the current state of research it is not possible to make a conclusive assessment of the effect of aromatherapy on pain, anxiety, sleep duration, and stress in children undergoing diagnostic and therapeutic procedures.

Background

Procedural pain is described as “the unpleasant sensory and emotional experience resulting from actual or potential tissue damage associated with diagnostic or therapeutic procedures”^[1]. Children perceive procedural pain as one of the most stressful and frightening experiences ever^[2]. The most common medical procedures used to diagnose and treat a disease can significantly cause pain and anxiety, especially in children^[3]. Pain perception heightens anxiety. In turn, anxiety may amplify the sensation of pain, creating a self-reinforcing cycle^[4]. The most common maladaptive responses in suboptimal pain and anxiety management are stress and sleep disturbances^[5]. Failure or inadequate management of symptomatology is associated with: (a) increased sensitivity to

future painful stimuli^[6]; (b) avoidance of medical care or failure to cooperate during the procedure^[7] or unsatisfactory treatment adherence^[8]; and (c) problems in cognitive and motor development and traumatic memories that may persist through adolescence and into adulthood^[9].

Drug therapy can be used to control pain and anxiety and to achieve good sleep quality. The use of analgesic drugs is an option to reduce pain, but potential side effects that children may experience include constipation, urinary retention, nausea, vomiting, sedation, respiratory depression, decreased heart rate, and blood pressure. In addition, the child may refuse to take the drugs^[10]. Topical anesthetics are also often unsuccessful because it may take long periods of time before the child feels the analgesic effect, or they may not be effective for every age group^[11]. Pharmacological methods to suppress anxiety include the use of sedatives, which, however, have

some side effects such as lethargy, development of rashes, dizziness, nausea, headache, and confusion^[12]. Sleep disorders are treated with sedative-hypnotic agents. They can significantly increase sleep duration but have side effects, cause dependence, and do not provide adequate sleep quality^[13]. In addition to side effects, pharmacological interventions do not always adequately control symptoms^[14]. Alleviating physical and psychological suffering during child-focused care is an ethical imperative, a child's right, and a nursing responsibility^[15] and is an integral part of quality health care^[16]. The approach to invasive procedures in the pediatric setting should include both pharmacological and nonpharmacological interventions; the latter should be used first^[17].

Nonpharmacological approaches, which are considered safer, could have a synergistic action when combined with drug therapy^[18]. Complementary medicine, which is growing rapidly in the industrialized world^[19], has in itself the potential to make an important contribution to the goal of achieving this goal. The Cochrane Collaboration's Complementary Medicine Field provides a definition of complementary medicine as "practices and ideas that are outside the domain of conventional medicine in different countries," defined by its users as "prevention or treatment of disease or promotion of health and well-being"^[20]. The definition is intentionally broad, as therapies considered as complementary practices in one country might be considered conventional in another^[21]. The key characteristic of complementary care is to have a holistic view of the person, a condition that for the nurse is akin to his or her professional attitude.

Aromatherapy is one of the most commonly practiced complementary therapies by nurses in hospitals, hospices, and community settings^[22]. In addition, it is identified as central to holistic nursing care^[23] as it recognizes the interconnectedness of the body, mind, emotions, spirit, and relationship with the individual^[24]. The delivery of aromatherapy within a patient-centered model is in line with the nursing theoretical foundations of Florence Nightingale, Martha Rogers, and Jean Watson, which hinged on promoting environmental and sensory influences on health, creating intentional and caring relationships, and recognizing the interrelationship between patients and caregivers, respectively^[25]. In the United Kingdom, aromatherapy is accepted and expected as part of nursing care^[26]. The Royal College of Nursing encourages nurses to use aromatherapy to improve nursing care. In fact, this practice could modify pain perception, reduce anxiety and stress, alleviate sleep disturbances, increase comfort, and provide relief on a spiritual level^[23]. In addition to this, compared with standard drug treatments, aromatherapy is convenient, easy to use, non-invasive, and has few side effects^[27].

The term "aromatherapy" was first coined by French chemist René-Maurice Gattefossé in the early 20th century; he discovered the healing properties of lavender oil in the

treatment of a burn^[28]. Aromatherapy is defined as "the competent and controlled use of essential oils for physical and emotional health and well-being"^[29]. It is a branch of phytotherapy that involves the use of essential oils, highly volatile, fragrant organic compounds obtained by the distillation of plant material derived from roots, leaves, bark, seeds, or flowers^[21]. These compounds are intended to help alleviate health problems and improve quality of life^[30]. The composition and potency of each essential oil can vary depending on the part of the plant from which it is extracted; chemically, it is a mixture of hydrocarbons, terpenes, phenols, and aldehydes^[31]. The chemical composition determines the therapeutic properties^[32].

The mechanism of action of aromatherapy is unclear. According to the most accepted hypothesis, inhalation of the molecules of essential oils would result in their absorption and distribution in the body by three different modes: 1) entry into the circulatory stream through the olfactory mucosa; 2) entry into the circulatory stream through the mucosa of the pulmonary alveoli; and 3) entry into the central nervous system through the olfactory system and the trigeminal nerve. With the last mode, the molecules would concentrate at the limbic system, of which the amygdala - involved in emotional memory systems, compares received stimuli with past experiences, and contributes to the processing of olfactory stimuli - and the hippocampus - involved in the formation and retrieval of learned memories and in short- and long-term olfactory memory - are of particular importance in aroma processing^[23]. Aroma molecules would produce brainstem release of neurotransmitters such as dopamine, norepinephrine, enkephalin, endorphins, and serotonin^[33], which would promote pain relief, anxiety and stress reduction, relaxation, sense of well-being, and sleep^[34].

The authors of a study^[25] designed to determine the prevalence of complementary and alternative medicine use among children with malignancies being treated at a large UK hospital found that aromatherapy constituted the most commonly used complementary therapy (68.8%). However, summary papers on the effect of aromatherapy on children are lacking in the literature. To our knowledge, there is only one systematic review^[36] evaluating the effectiveness of aromatherapy in pediatric settings. However, the authors (a) included both primary and secondary studies published between 2010 and 2020; (b) this studies focused exclusively on the efficacy of inhalation aromatherapy applied to hospitalized children and (c) did not analyze the references of the included papers or consult the gray literature. It is considered important to undertake a study with quantitative synthesis that would extend and update knowledge on the effect of aromatherapy in terms of efficacy and safety, in light of its increasingly widespread use in pediatric settings. The results obtained could prove valuable in maximizing its therapeutic effect and reducing its possible adverse effects.

Objective

To assess the effectiveness of aromatherapy in reducing procedural pain, anxiety, stress-related physiological responses, and in improving sleep duration among pediatric patients undergoing diagnostic or therapeutic procedures.

Methods

To achieve the objective, a systematic review with meta-analysis adhering to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement^[37] was conducted. The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42025642105).

Inclusion criteria

The following inclusion criteria were considered: (a) population: subjects aged 0-18 years to undergo any type of diagnostic and curative treatment in any setting; (b) intervention: aromatherapy, delivered by inhalation, nebulizer, or massage, alone or in combination with minimal intervention (e.g., musical background, colorful drawings); (c) comparison: standard care or placebo; (d) outcomes (assessed by any type of instrument) – primary: pain (detected at the end of the procedure), anxiety (detected at the end of the procedure), sleep duration (detected on the first night), reported by the child or a healthcare professional or researcher; secondary – duration of crying, heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, percent blood oxygen saturation, salivary cortisol levels, as proxy parameters of the stress condition; (e) study design: randomized clinical trials (RCTs) or quasi-randomized controlled trials (qRCTs) with parallel groups that evaluated at least one of the outcomes, primary or secondary, of interest. Crossover studies were also included provided that data from both groups were available. In the case of multiple comparisons in the same study, these comparisons were treated as independent.

Search strategy

The document search was performed on January 7, 2025. The biomedical databases The Cochrane Library, MEDLINE (via PubMed), EMBASE (via Elsevier), CINAHL (via EBSCOhost), PsycINFO (via Ovid), Web of Science (via Clarivate Analytics), and Scopus (via Elsevier) were queried. ClinicalTrials.gov was consulted to identify completed studies with available but not yet published data, and the Google Scholar web resource to identify unpublished studies. Leading journals were also consulted (Complementary Therapies in Medicine, Complementary Therapies in Clinical Practice, Holistic Nursing Practice, BMC Complementary and Alternative Medicine, Evidence-Based Complementary and Alternative Medicine, International Journal of Pediatrics and Child Health, International Journal of Clinical Pediatrics and Child Health, Paediatrics and International Child Health). Finally, references of available reviews and eligible studies were analyzed. No publication date limits were imposed; only papers written in

English or Italian were considered. The search strategy used for the different resources queried is shown in Appendix.

Study selection and data extraction

Two authors (VA and SCR) independently selected the records after reading the title and abstract. Full texts of the records considered relevant were retrieved and, again independently, two authors (CC and VT) analyzed and evaluated them. Any disagreements were overcome by comparison and discussion; if no agreement was reached, arbitration by another author (MD) was requested. Three authors (CR, SM, and BB), independently and using a shared and standardized model implemented in tabular form on Microsoft Excel 2016, extracted the following information and data from the included studies: first author, year of publication, and country; setting; study design; procedure; sample characteristics (total and per-group numerosity, mean age or age range, percentage of males); type of fragrance used and mode of delivery; type of control; list of outcomes analyzed; and primary outcome assessment tools.

Risk of bias

Independently, two authors (LGR and MD) assessed the risk of bias of randomized controlled trials with the Revised Cochrane Risk Of Bias tool for randomized trials (RoB 2)^[38]. Any disagreement was resolved by comparison and discussion; if no agreement was reached, arbitration by another author (BB) was requested. RoB 2 is a tool that examines the internal validity of randomized controlled clinical trials and is structured into domains through which systematic errors (biases) could be introduced. The domains are named after the study phase in which the risk of bias could occur: (1) b. in the randomization process; (2) b. for a deviation from the planned intervention; (3) b. for missing data; (4) b. in the measurement of outcomes; and (5) b. in the selection of reported outcomes. Ascertaining the risk of bias is done with reporting questions within decision algorithms; based on the answers given, one of the following judgments can be obtained for each domain: (a) low risk; (b) some concern; (c) high risk. Overall, a study's risk of bias is judged low if all domains are at low risk of bias, with some concerns if at least one of the domains raises some concerns, and high if at least one domain is at high risk of bias.

The risk of bias of quasi-randomized controlled clinical trials was assessed with the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)^[39] by two authors (BB and MD) independently. Any disagreements were resolved by comparison and discussion, but arbitration by another author (LGR) was used when necessary. ROBINS-I is a tool that analyzes the internal validity of nonrandomized or quasi-randomized controlled clinical trials and is also structured into domains through which bias could be introduced. The domains are divided according to the stage of intervention delivery: (1) before the intervention (b. for confounding, b. in participant selection); (2) at the time of the intervention (b. in intervention classification); (3) after the intervention (b. for deviations from intended interventions, b. for missing data, b.

in outcome measurement, b. in selection of reported outcomes). Ascertaining the risk of bias is done with reporting questions within decision algorithms; based on the answers given, one of the following judgments can be obtained for each bias: (a) low risk; (b) moderate risk; (c) serious risk; (d) critical risk. Overall, a study's risk of bias is judged as low if all domains are at low risk of bias; moderate if the domains are at low or moderate risk of bias; serious if at least one of the domains is at serious risk of bias; and critical if at least one domain is at critical risk of bias.

Data analysis and synthesis

Estimation of the overall mean effect of the intervention was calculated by meta-analysis using a random-effects model under the assumption of significant heterogeneity among studies and producing forest plots in the case of at least two studies per outcome. The standardized mean difference (SMD) for continuous measures was calculated using Cohen's d: as a function of values of 0.2, 0.5, or 0.8^[40], the effect size was assumed to be small, moderate, or large, respectively. In the case of "negative" standardized mean differences, this means that there was an improvement in the intervention group. For outcomes measured with the same assessment tool, the unstandardized mean difference (UMD) was calculated. For the calculation of the deviation from the point estimate of the effect for each individual study and the overall estimate for the aggregated studies, a 95% confidence interval (CI) was considered. The presence of heterogeneity among studies was assessed with the Cochran Q test^[41]; the level of heterogeneity was calculated with the Higgins I² index^[42]. A low, moderate, high, or very high level was assigned to values of I² ≤ 30%, 30% < I² ≤ 60%, 60% < I² ≤ 90%, or I² > 90%, respectively^[43]. Data processing was performed with ProMeta[©] version 3.0 software.

Additional analyses

On the outcome "pain," subgroup analyses were conducted according to: (a) age group, (b) procedure, (c) mode of intervention delivery, and (d) type of fragrance.

Sensitivity analysis

Also on the outcome "pain," a sensitivity analysis was performed by regenerating the meta-analysis after the exclusion of quasi-randomized studies.

Publication bias

In the case of at least ten included studies, the funnel plot^[44] was created, and the Trim and Fill method^[45] was applied for a qualitative analysis of the risk of publication bias. A quantitative assessment was performed using Egger's test^[46] and Begg and Mazumdar's test^[47].

Quality/certainty of evidence

Independently, three authors (LGR, VT, and BB) performed the overall assessment of certainty/quality of evidence by generating a summary of findings table in compliance with the GRADE method^[48]. Comparison and discussion guided the handling of any disagreements; if conflicting opinions persisted, arbitration by another author (MD) was requested.

Results

Selection of studies

The implementation of the search strategy led to the retrieval of 213 records; Figure 1 shows the screening process.

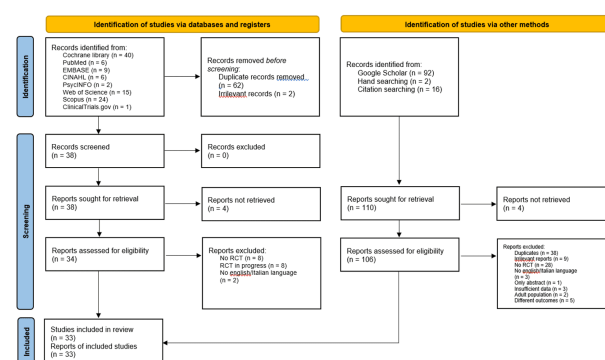


Figure 1. Record screening process.

At the end of the screening process, 33 studies^{[10][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76][77][78][79][80]} were included in the systematic review, which were matched by as many reports for a total of 49 comparisons.

Table 1 shows the main characteristics of the included studies.

Study (year)	Country	Setting	Study design	Procedure	Sample	Fragrance (delivery method)	Control	Outcomes	Primary outcome assessment tools
Abdالحاي ^[49]	Syria	Pediatric dental clinic	RCT	Local anesthesia pre-treatment for dental caries	N = 56 (IG (aromatherapy + music) = 28, CG = 28), mean age 8 yrs, males 55%	Lavender and Neroli (inhalation)	Placebo	Pain, anxiety (*), heart rate, systolic arterial pressure, diastolic arterial pressure, percentage saturation of oxygen in the blood (*) incomplete data	Anxiety - Facial Image Scale (FIS) Pain - Face-Legs - Activity-Cry-Consolability (FLACC)
Afshar ^[50]	Iran	Pediatrics department	RCT	Venipuncture	N = 30 (IG 1 (aromatherapy) = 10, IG 2 (puppet) = 10, CG = 10), mean age 5.2 yrs	Lavender (inhalation)	Standard care	Pain	Oucher Pain Scale (OPS)
Ahmed ^[51]	Egypt	Pediatrics department	qRCT	Surgical intervention	N = 100 (IG = 50, CG = 50), mean age 8.3 yrs, males 71%	Lavender (massage)	Standard care	Pain, sleep	Pain - Wong-Baker Faces Pain Rating Scale (WBFPRS) Sleep - Pittsburgh Sleep Quality Index (PSQI)
Akgül ^[52]	Turkey	Pediatric burns unit	RCT	Burn dressing	N = 108 (IG 1 (lavender for 15') = 36, IG 2 (lavender for 60') = 36, CG = 36), mean age 3.1 yrs	Lavender (inhalation)	Placebo	Pain, heart rate, mean arterial pressure, respiratory rate, body temperature	Face-Legs - Activity-Cry-Consolability (FLACC)
Alemdar ^[53]	Turkey	Pediatric clinic	RCT	Venipuncture	N = 195 (IG 1 (buzzy) = 39, IG 2 (lidocaine) = 39, IG 3 (soap bubbles) = 39, IG 4 (aromatherapy) = 39, CG = 39), mean age 7.3 yrs, males 54%	Lavender (inhalation)	Standard care	Pain, fear, distress, salivary cortisol level	Oucher Pain Scale (OPS)
Ali ^[54]	Egypt	Vaccination center	qRCT	Vaccination	N = 120 (IG = 60, CG = 60), mean age 5.1 months, males 53%	Lavender (massage)	Standard care	Pain, duration of crying	Modified Behavioral Pain Scale (MBPS)

Study (year)	Country	Setting	Study design	Procedure	Sample	Fragrance (delivery method)	Control	Outcomes	Primary outcome assessment tools
Ariani ^[55]	Indonesia	Pediatric department	qRCT	Intravenous cannulation	N = 24 (IG = 12, CG = 12), mean age 9 yrs, males 63%	Peppermint (inhalation)	Standard care	Pain	Wong–Baker Faces Pain Rating Scale (WBFPRS)
Arslan ^[56]	Turkey	Pediatric dental clinic	RCT	Extraction of deciduous mandibular molar tooth	N = 126 (IG = 63, CG = 63), mean age 8.8 yrs, males 57%	Lavender (inhalation)	Standard care	Anxiety (*), pain (*), heart rate, systolic arterial pressure, diastolic arterial pressure, percentage saturation of oxygen in the blood (*) incomplete data	Anxiety - Facial Image Scale (FIS) Pain - Face-Legs - Activity-Cry-Consolability (FLACC) and Wong–Baker Faces Pain Rating Scale (WBFPRS)
Bikmoradi ^[57]	Iran	Pediatric department	qRCT	Intravenous cannulation	N = 60 (IG = 30, CG = 30), mean age 4.5 yrs, males 40%	Lavender (inhalation)	Standard care	Pain	Oucher Pain Scale (OPS)
Çetinkaya ^[58]	Turkey	Pediatric clinic	qRCT	Abdominal colic treatment	N = 40 (IG = 20, CG = 20), mean age 25.7 yrs, males 43%	Lavender (massage)	Standard care	Duration of crying	-
de Jong ^[59]	Netherlands	Pediatric Intensive Care Unit	RCT	Surgical intervention	N = 59 (IG 1 (aromatherapy) = 20, IG 2 (placebo) = 20, CG = 19), mean age 10.8 months, males 75%	Mandarin (massage)	Standard care	Pain	COMFORT-B Scale (CBS)
Elsayed ^[60]	Egypt	Pediatric surgical department	qRCT	Surgical intervention	N = 100 (IG = 50, CG = 50), mean age 9.4 yrs, males 71%	Lavender (massage)	Standard care	Pain, sleep	Pain - Wong–Baker Faces Pain Rating Scale (WBFPRS) Sleep - Pittsburgh Sleep Quality Index (PSQI)
Ghaderi ^[61]	Iran	Pediatric dental clinic	RCT crossover	Alveolar nerve block and dental caries treatment	N = 24 (IG = 12, CG = 12), mean age 8 yrs	Lavender (nebulizer)	Placebo	Pain, heart rate, salivary cortisol level	Wong–Baker Faces Pain Rating Scale (WBFPRS) and Face-Legs - Activity-Cry-Consolability (FLACC)

Study (year)	Country	Setting	Study design	Procedure	Sample	Fragrance (delivery method)	Control	Outcomes	Primary outcome assessment tools
Jafarzadeh ^[62]	Iran	Pediatric dental clinic	RCT crossover	Permanent molar fissure sealing	N = 30 (IG = 15, CG = 15), mean age 7.7 yrs, males 33.3%	Sweet orange (nebulizer)	Placebo	Heart rate, salivary cortisol level	-
James ^[63]	India	Pediatric dental clinic	qRCT	Restorative dental treatment	N = 150 (IG 1 (aromatherapy) = 50, IG 2 (music) = 50, CG = 50)	Orange (nebulizer)	Standard care	Anxiety (*), heart rate, respiratory rate, percentage saturation of oxygen in the blood (*) incomplete data	-
Janthasila ^[64]	Thailandia	Pediatric dental clinic	RCT	Dental treatment	N = 128 (IG 1 (music) = 33, IG 2 (aromatherapy) = 31, IG 3 (music + aromatherapy) = 32, CG = 32), mean age 11 yrs, males 58%	Lavender (nebulizer)	Placebo	Anxiety, heart rate, systolic arterial pressure, diastolic arterial pressure, percentage saturation of oxygen in the blood	Facial Image Scale (FIS)
Khattab ^[65]	Egitto	Pediatric dental clinic	qRCT	Tooth Extraction	N = 60 (IG 1 (aromatherapy) = 20, IG 2 (audiovisual distraction) = 20, CG = 20), mean age 6.7 yrs, males 43%	Lavender (inhalation)	Standard care	Anxiety, pain, heart rate, respiratory rate	Anxiety - RMS Pictorial Scale (RMS-PS) Pain - Face-Legs - Activity-Cry-Consolability (FLACC)
Marofi ^[66]	Iran	Pediatric surgical department	qRCT	Surgical intervention	N = 64 (IG = 32, CG = 32), mean age 4.4 yrs, males 72%	Damask rose (inhalation)	Placebo	Pain	Toddler Preschooler Postoperative Pain Scale (TPPPS)
Ndao ^[67]	United States	Pediatric oncology department	RCT	Stem cell infusion	N = 37 (IG = 17, CG = 20), mean age 12.3 yrs, males 73%	Bergamot (nebulizer)	Placebo	Anxiety, pain, nausea	Anxiety - State-Trait Anxiety Inventory for Children (STAIC) Pain - Visual Analogue Scale (VAS)
Nirmala ^[68]	India	Pediatric dental clinic	RCT	Local anesthesia for dental treatment	N = 150 (IG 1 (lavender with nebulizer) = 30, IG 2 (lavender inhaled) = 30, IG 3 (orange with nebulizer) = 30, IG 4	Orange (inhaled or with nebulizer) Lavender (inhaled or with nebulizer)	Standard care	Anxiety, pain, heart rate	Anxiety - Modified Child Dental Anxiety Scale - Faces version (MCDAS(f)) Pain - Face-

Study (year)	Country	Setting	Study design	Procedure	Sample	Fragrance (delivery method)	Control	Outcomes	Primary outcome assessment tools
					(orange inhaled) = 30, CG = 30), mean age 9.6 yrs, males 56%				Legs - Activity-Cry-Consolability (FLACC)
Nord ^[69]	United States	Pediatric surgical department	RCT	Surgical intervention	N = 94 (IG = 48, CG = 46), age < 21 yrs	Lavender and ginger (inhalation and topical application)	Placebo	Pain	Face-Legs - Activity-Cry-Consolability (FLACC)
Omer ^[70]	Egypt	Pediatric dental clinic	RCT	Extraction of deciduous mandibular molar tooth	N = 45 (IG 1 (lemongrass) = 15, IG 2 (rosemary) = 15, CG = 15), mean age 6.7 yrs, males 43%	Lemongrass (inhalation) Rosemary (inhalation)	Standard care	Anxiety, systolic arterial pressure, diastolic arterial pressure, percentage saturation of oxygen in the blood	Anxiety - Wong-Baker Faces Pain Rating Scale (WBFPRS)
Razaghi ^[71]	Iran	Neonatology department	qRCT	Venipuncture	N = 120 (IG 1 (lavender) = 40, IG 2 (glucose) = 40, CG = 40), mean age 5.5 days, males 40%	Lavender (inhalation)	Standard care	Pain, duration of crying	Pain - Douleur Aigue du Nouveau-né (DAN)
Rehim ^[72]	Egypt	Pediatric dental clinic	RCT	Deciduous molar pulp therapy	N = 100 (IG 1 (lavender) = 25, IG 2 (chamomile) = 25, IG 3 (peppermint) = 25, CG = 25), mean age 6.9 yrs	Lavender (nebulizer) Chamomile (nebulizer) Peppermint (nebulizer)	Standard care	Anxiety, heart rate, percentage saturation of oxygen in the blood	Animated emoji scale
Renani ^[73]	Iran	Pediatric oncology department	qRCT	Antineoplastic treatment	N = 60 (IG = 30, CG = 30)	Sweet orange (nebulizer)	Placebo	Sleep	Children's Sleep Habits Questionnaire (CSHQ)
Romantsik ^[74]	Estonia	Neonatology department	qRCT	Capillary sampling	N = 69 (IG = 39, CG = 30), mean age 1.8 days, males 49%	Vanilla (inhalation)	Placebo	Pain, duration of crying	Behavioral Indicators of Infant Pain Scale (BIIPS)
Salarfard ^[75]	Iran	Pediatric department	qRCT	Invasive treatments	N = 70 (IG = 35, CG = 35), range of age 6-12 yrs, males 53%	Sweet orange (inhalation)	Standard care	Sleep	Bedtime Problems, Excessive Daytime Sleepiness, Awakenings during the night; Regularity of sleep/wake cycles; and

Study (year)	Country	Setting	Study design	Procedure	Sample	Fragrance (delivery method)	Control	Outcomes	Primary outcome assessment tools
									Snoring (BEARS)
Sharifi ^[76]	Iran	Community	qRCT	Invasive treatments for type 1 diabetes mellitus management	N = 60 (IG = 30, CG = 30), mean age 9.3 yrs, males 58%	Sweet orange (inhalation)	Standard care	Anxiety	State-Trait Anxiety Inventory for Children (STAIC)
Soltani ^[77]	Iran	Pediatric surgical department	RCT	Tonsillectomy	N = 48 (IG = 24, CG = 24), mean age 7.3 yrs, males 56%	Lavender (inhalation)	Standard care	Pain, night awakenings	Visual Analogue Scale (VAS)
Soni ^[78]	India	Pediatric dental clinic	RCT	Restoration with glass ionomer cement	N = 30 (IG = 15, CG = 15), mean age 7.4 yrs, males 50%	Sweet orange (inhalation)	Standard care	Anxiety, heart rate, systolic arterial pressure, diastolic arterial pressure, percentage saturation of oxygen in the blood	Venham Picture Test (VPT)
Triana ^[10]	Indonesia	Pediatric oncology department	qRCT	Management of chronic pain induced by neoplasia	N = 20 (IG = 10, CG = 10), mean age 12.2 yrs, males 55%	Various (inhalation)	Standard care	Pain	Visual Analogue Scale (VAS)
Vaziri ^[79]	Iran	Vaccination center	RCT	Vaccination	N = 97 (IG = 43, CG = 54)	Lavender (inhalation)	Placebo	Pain, duration of crying	Neonatal Infant Pain Scale (NIPS)
Yadav ^[80]	India	Pediatric dental clinic	qRCT	Local anesthesia for dental treatment	N = 176 (IG = 88, CG = 88), mean age 7.3 yrs, males 50%	Sweet orange (nebulizer)	Standard care	Anxiety, pain	Anxiety - Modified Child Dental Anxiety Scale - Faces version (MCDAS(f)) Pain - Sound-Eye-Motor (SEM) scale and Visual Analogue Scale (VAS) and Wong-Baker Faces Pain Rating Scale (WBFPRS)

Table 1. Main characteristics of the included studies.

CG = Control Group; IG = Intervention Group; qRCT = quasi- Randomized Controlled Trial; RCT = Randomized Controlled Trial.

Main characteristics of the included studies

The studies were published between 2009 and 2024; eleven were conducted in Iran^{[50][57][61][62][66][71][73][75][76][77][79]}, six in Egypt^{[51][54][60][65][70][72]}, four in India^{[63][68][78][80]}, four in Turkey^{[52][53][56][58]}, two in Indonesia^{[10][55]}, two in the United States^{[67][69]}, one in Estonia^[74], one in Thailand^[64], one in the Netherlands^[59], and finally one in Syria^[49]. Twelve studies were conducted in a pediatric dental clinic^{[49][56][61][62][63][64][65][68][70][72][78][80]}, five in a pediatric department^{[50][51][55][57][75]}, four in a pediatric surgical department^{[60][66][69][77]}, three in a pediatric oncology department^{[10][63][67]}, two in a vaccination center^{[54][79]}, two in a pediatric outpatient clinic^{[53][58]}, two in a neonatal ward^{[71][74]}, one in the community^[76], one in a pediatric burn unit^[52], one in a pediatric intensive care unit^[59]. Sixteen studies are quasi-randomized controlled trials^{[10][51][54][55][57][58][60][63][65][66][71][73][74][75][76][80]}, the others are randomized controlled trials with parallel groups, except for two^{[61][62]} that are crossover. The most frequent procedures included dental care, venipuncture, capillary sampling, intravenous cannulation, vaccine inoculation, and surgery. The studies included a total of 2650 children, with a mean age ranging from 1.8 days^[74] to 12.3 years^[67]; the proportion of males ranged from 33.3%^[62] to 75%^[59]. The minimum sample size of the studies is 20 subjects^[10], and the maximum sample size is 195 subjects^[53]. The most common exclusion criteria were the presence of unstable hemodynamic conditions, sensory or cognitive disabilities, and established fragrance allergies.

Aromatherapy delivery was carried out in 19 studies by direct inhalation^{[10][49][50][52][53][55][56][57][65][66][68][69][70][71][75][76][77][78][79]}, in nine studies by inhalation through a room nebulizer^{[61][62][63][64][67][68][72][73][74]}, and in seven studies through massage, using a carrier oil as a base^{[51][54][58][59][60][69][80]}.

In 18 studies, lavender was the most commonly used fragrance^{[49][50][51][52][53][54][55][56][57][58][60][61][64][65][69][71][72][77][79]}, followed in seven studies by sweet orange^{[61][62][68][73][75][76][78]}. The control group was given a placebo (N = 11) or standard care (N = 22).

The studies made 49 comparisons; of these, 39 involved aromatherapy vs standard care or placebo. Twenty-two

studies with 27 comparisons assessed pain^{[10][49][50][51][52][53][54][55][57][59][60][61][65][66][67][68][69][71][74][77][79][79][80]}, nine studies with 15 comparisons anxiety^{[64][65][67][68][70][72][72][76][78][80]}, four studies for as many comparisons sleep duration^{[51][60][73][75]}, five studies for as many comparisons crying duration^{[54][58][71][74][79]}, 12 studies with 21 comparisons heart rate^{[49][52][56][61][62][63][64][65][68][70][72][78]}, five studies and six comparisons systolic and diastolic blood pressure^{[49][56][64][70][78]}, three studies and four comparisons respiratory rate^{[52][63][65]}, seven studies and 10 comparisons percent blood oxygen saturation^{[49][56][63][64][70][72][78]}, and finally three studies and five comparisons salivary cortisol level^{[53][61][62]}.

For pain measurement, the studies used a total of 11 assessment tools: Behavioral Indicators of Infant Pain Scale (BIIPS)^[81], COMFORT-B Scale (CBS)^[82], Douleur Aigue du Nouveau-né (DAN)^[83], Face-Legs-Activity-Cry-Consolability (FLACC)^[84], Modified Behavioral Pain Scale (MBPS)^[85], Neonatal Infant Pain Scale (NIPS)^[86], Oucher Pain Scale (OPS)^[87], Sound-Eye-Motor (SEM) scale^[88], Toddler Preschooler Postoperative Pain Scale (TPPPS)^[89], Visual Analogue Scale (VAS)^[90], Wong-Baker Faces Pain Rating Scale (WBFPRS)^[91]. Anxiety was measured with seven different assessment instruments: Animated emoji scale^[72], Facial Image Scale (FIS)^[92], Modified Child Dental Anxiety Scale Faces version (MCDAS(f))^[93], RMS Pictorial Scale (RMS-PS)^[94], State-Trait Anxiety Inventory for Children (STAIC)^[95], Venham Picture Test (VPT)^[96], Wong-Baker Faces Pain Rating Scale (WBFPRS)^[91]. Finally, sleep duration was measured using three assessment instruments: Bedtime Problems, Excessive Daytime Sleepiness, Awakenings during the night, Regularity of sleep/wake cycles and Snoring (BEARS)^[97], Children's Sleep Habits Questionnaire (CSHQ)^[98], Pittsburgh Sleep Quality Index (PSQI)^[99].

Risk of Bias

Figure 2 illustrates the risk of bias of the 17 RCTs included with the Risk of Bias 2 tool. Overall, the risk of bias is high for nine studies^{[49][50][53][61][62][64][68][77][78]}, raises some concerns for five^{[52][56][69][70][79]} and is low for three^{[59][69][72]}.

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Abdalhai 2024	<div>-</div>	<div>✗</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>✗</div>
	Afshar 2020	<div>-</div>	<div>✗</div>	<div>+</div>	<div>✗</div>	<div>-</div>	<div>✗</div>
	Akgül 2021	<div>-</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>-</div>
	Alemdar 2019	<div>-</div>	<div>-</div>	<div>+</div>	<div>✗</div>	<div>-</div>	<div>✗</div>
	Arslan 2020	<div>-</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>-</div>	<div>-</div>
	de Jong 2012	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>
	Ghaderi 2020	<div>✗</div>	<div>✗</div>	<div>+</div>	<div>✗</div>	<div>+</div>	<div>✗</div>
	Jafarzadeh 2013	<div>✗</div>	<div>-</div>	<div>+</div>	<div>✗</div>	<div>+</div>	<div>✗</div>
	Janthasila 2023	<div>✗</div>	<div>-</div>	<div>+</div>	<div>✗</div>	<div>+</div>	<div>✗</div>
	Ndao 2012	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>
	Nirmala 2021	<div>+</div>	<div>-</div>	<div>+</div>	<div>✗</div>	<div>-</div>	<div>✗</div>
	Nord 2009	<div>-</div>	<div>-</div>	<div>+</div>	<div>+</div>	<div>-</div>	<div>-</div>
	Omer 2024	<div>+</div>	<div>+</div>	<div>+</div>	<div>-</div>	<div>+</div>	<div>-</div>
	Rehim 2024	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>
	Soltani 2013	<div>✗</div>	<div>-</div>	<div>+</div>	<div>-</div>	<div>-</div>	<div>✗</div>
	Soni 2018	<div>-</div>	<div>-</div>	<div>+</div>	<div>✗</div>	<div>-</div>	<div>✗</div>
Vaziri 2019	<div>-</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>-</div>	
Domains:		Judgement					
D1: Bias arising from the randomization process.		<div>✗</div> High					
D2: Bias due to deviations from intended intervention.		<div>-</div> Some concerns					
D3: Bias due to missing outcome data.		<div>+</div> Low					
D4: Bias in measurement of the outcome.							
D5: Bias in selection of the reported result.							

Figure 2. RoB 2.

Figure 3 illustrates the risk of bias of the 16 qRCTs included with the ROBINS-I tool. Overall, there are 15 studies at serious risk of bias^{[10][51][54][55][57][58][60][63][65][71][73][74][75][76][80]}, while one is at moderate risk of bias^[66].

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Ahmed 2019								
	Ali 2021								
	Ariani 2020								
	Bikmoradi 2017								
	Çetinkaya 2012								
	Elsayed 2023								
	James 2021								
	Khattab 2022								
	Marofi 2015								
	Razaghi 2020								
	Renani 2023								
	Romantsik 2014								
	Salarfard 2023								
	Sharifi 2017								
	Triana 2022								
	Yadav 2024								

Domains:

D1: Bias due to confounding.

D2: Bias due to selection of participants.

D3: Bias in classification of interventions.

D4: Bias due to deviations from intended interventions.

D5: Bias due to missing data.

D6: Bias in measurement of outcomes.

D7: Bias in selection of the reported result.

Judgement

Serious

Moderate

Low

Figure 3. ROBINS-I.

Primary outcomes

Pain: aromatherapy vs. control

The effect of aromatherapy on pain compared with control was evaluated in 1794 participants (27 comparisons, 22 studies). The effect size of the intervention is large: SMD = -1.12 (95% CI: -1.60, -0.65) in favor of the intervention in a statistically significant way. Statistical heterogeneity is significant ($Q = 526.40$, $p = 0.000$) and very high ($I^2 = 95.06\%$) (Table 2).

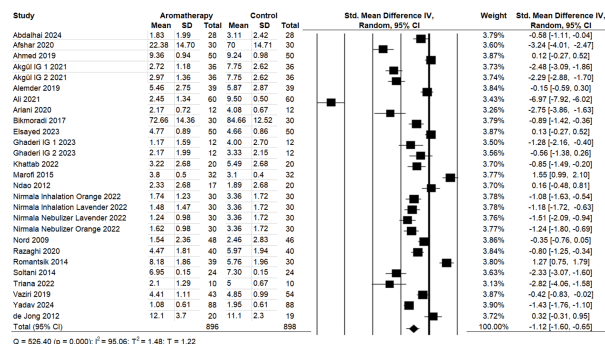


Table 2. Pain: aromatherapy vs. control. Anxiety: aromatherapy vs. control

The effect of aromatherapy on anxiety compared with control was evaluated in 856 participants (15 comparisons, nine studies). The effect size of the intervention is large: SMD = -1.08 (95% CI: -1.52, -0.64) in favor of the intervention in a statistically significant way. Statistical heterogeneity is significant ($Q = 118.73$, $p = 0.000$) and high ($I^2 = 88.21\%$) (Table 3).

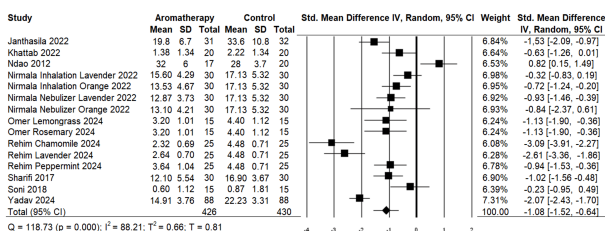


Table 3. Anxiety: aromatherapy vs. control. Sleep duration: aromatherapy vs. control

The effect of aromatherapy on sleep duration compared to control was evaluated in 330 participants (four studies). The effect size of the intervention is large: SMD = -0.95 (95% CI: -1.94, 0.03) in favor of the intervention in a statistically not significant way. Statistical heterogeneity is significant ($Q = 51.95$, $p = 0.000$) and very high ($I^2 = 94.23\%$) (Table 4).

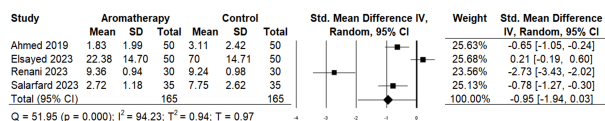


Table 4. Sleep duration: aromatherapy vs. control.

Secondary outcomes

Crying duration: aromatherapy vs. control

The effect of aromatherapy on crying duration compared to control was assessed in 406 participants (five studies). The unstandardized mean difference is equal to UMD = -28.93 seconds (95% CI: -46.42 seconds, -11.44 seconds) in favor of the intervention in a statistically significant way (see Appendix). Statistical heterogeneity is significant ($Q = 79.87$, $p = 0.000$) and very high ($I^2 = 94.99\%$).

Heart rate: aromatherapy vs. control

The effect of aromatherapy on heart rate compared to control was assessed in 1117 participants (21 comparisons, 12 studies). The unstandardized mean difference is equal to UMD = -12.43 beats per minute (95% CI: -15.69 beats per minute, -9.17 beats per minute) in favor of the intervention in a statistically significant way (see Appendix). Statistical heterogeneity is significant ($Q = 201.67$, $p = 0.000$) and very high ($I^2 = 90.08\%$).

Systolic blood pressure: aromatherapy vs. control

The effect of aromatherapy on systolic blood pressure compared to control was evaluated in 335 participants (six comparisons, five studies). The unstandardized mean difference is equal to UMD = -6.38 mmHg (95% CI: -8.57 mmHg, -4.20 mmHg) in favor of the intervention in a statistically significant way (see Appendix). Statistical heterogeneity is not significant ($Q = 2.98$, $p = 0.703$).

Diastolic blood pressure: aromatherapy vs. control

The effect of aromatherapy on diastolic blood pressure compared to control was evaluated in 335 participants (six comparisons, five studies). The unstandardized mean difference is equal to UMD = -8.89 mmHg (95% CI: -11.89 mmHg, -5.88 mmHg) in favor of the intervention in a statistically significant way (see Appendix). Statistical heterogeneity is significant ($Q = 15.66$, $p = 0.008$) and high ($I^2 = 68.06\%$).

Respiratory rate: aromatherapy vs. control

The effect of aromatherapy on respiratory rate compared to control was evaluated in 284 participants (four comparisons, three studies). The unstandardized mean difference is equal to UMD = -3.39 breaths per minute (95% CI: -5.57 breaths per minute, -1.20 breaths per minute) in favor of the intervention in a statistically significant way (see Appendix). Statistical

heterogeneity is significant ($Q = 74.39$, $p = 0.008$) and very high ($I^2 = 95.97\%$).

Percentage oxygen saturation in the blood: aromatherapy vs. control

The effect of aromatherapy on the percentage oxygen saturation in the blood compared to the control was evaluated in 584 participants (10 comparisons, seven studies). The unstandardized mean difference is equal to $UMD = 0.48$ SatO₂% (95% CI: 0.02 SatO₂%, 0.95 SatO₂%) in favor of the intervention in a statistically significant way (see Appendix). Statistical heterogeneity is significant ($Q = 71.54$, $p = 0.000$) and high ($I^2 = 87.42\%$).

Salivary cortisol level: aromatherapy vs. control

The effect of aromatherapy on the salivary cortisol level compared to the control was evaluated in 186 participants (five comparisons, three studies). The effect size of the intervention is moderate: $SMD = -0.69$ (95% CI: -1.16, -0.23) in favor of the intervention in a statistically significant way (see Appendix). Statistical heterogeneity is not significant ($Q = 8.64$, $p = 0.071$) and moderate ($I^2 = 53.72\%$).

In summary, the results of the meta-analysis pointed out that aromatherapy produced a large effect size on pain, anxiety and sleep duration. By converting SMD to NNT, it is possible to provide clinical meaning to the results obtained: for pain $SMD = -1.12$ equals $NNT = 1.749$, for anxiety $SMD = -1.08$ equals $NNT = 1.802$, and for sleep duration $SMD = -0.95$ equals $NNT = 2.007$. This is equivalent to saying that for every two children treated with aromatherapy, one child will have less pain or anxiety or sleep longer. In addition, considering for example the physiological parameters of a child aged 8 years as baseline values, aromatherapy clinically significantly reduced heart rate (11%), systolic blood pressure (5%), diastolic blood pressure (12%), and respiratory rate (12%). Finally, aromatherapy increased clinically not significantly blood oxygen saturation (0.5%), had a moderate effect size on salivary cortisol concentration ($SMD = -0.69$, which equals $NNT = 2.671$ - for every 16 children treated with aromatherapy, a reduction in salivary cortisol concentration will be observed in 6 children), and reduced the duration of crying by almost 30 seconds.

Additional analyses

Age range

Depending on the availability of the mean age of participants (20 studies, $N = 1564$), studies that addressed pain were assigned to the subgroup "infants" (0-2 years) ($N = 269$), "preschool children" (3-5 years) ($N = 328$), or "school children" (6-12 years) ($N = 967$). For the 0-2 years subgroup, the effect size of the intervention is large: $SMD = -2.14$ (95% CI: -5.76, 1.48) in favor of the intervention in a statistically non-significant manner. Statistical heterogeneity is significant ($Q = 221.91$, $p = 0.000$) and very high ($I^2 = 99.10\%$). For the 3-5 years subgroup, the effect size of the intervention is large: $SMD =$

-1.46 (95% CI: -3.12, 0.20) in favor of the intervention in a statistically non-significant manner. Statistical heterogeneity is significant ($Q = 150.67$, $p = 0.000$) and very high ($I^2 = 97.30\%$). For the 6-12 years subgroup, the effect size of the intervention is large: $SMD = -1.00$ (95% CI: -1.41, -0.60) in favor of the intervention in a statistically significant way. Statistical heterogeneity is significant ($Q = 125.43$, $p = 0.000$) and high ($I^2 = 88.04\%$) (see Appendix).

Procedure

Based on the type of procedure performed on the participants, the studies that treated pain were assigned to the subgroup "non-dental procedure" ($N = 1234$) or "dental procedure" ($N = 560$). For the first subgroup, the effect size of the intervention is large: $SMD = -1.17$ (95% CI: -1.86, -0.47) in favor of the intervention in a statistically significant way. Statistical heterogeneity is significant ($Q = 485.97$, $p = 0.000$) and very high ($I^2 = 96.50\%$). For the second subgroup, the effect size of the intervention is large: $SMD = -1.12$ (95% CI: -1.35, -0.90) in favor of the intervention in a statistically significant way. Statistical heterogeneity is not significant ($Q = 11.72$, $p = 0.164$) and moderate ($I^2 = 31.74\%$) (see Appendix).

Mode of delivery

Based on the mode of aromatherapy delivery, studies that treated pain were assigned to the subgroup "inhalation" ($N = 1054$), "massage" ($N = 359$), or "nebulizer" ($N = 381$). For the "inhalation" subgroup, the effect size of the intervention is large: $SMD = -1.09$ (95% CI: -1.66, -0.52) in favor of the intervention in a statistically significant way. Statistical heterogeneity is significant ($Q = 277.85$, $p = 0.000$) and very high ($I^2 = 94.24\%$). For the "massage" subgroup, the effect size of the intervention is large: $SMD = -1.55$ (95% CI: -3.69, 0.59) in favor of the intervention in a statistically non-significant way. Statistical heterogeneity is significant ($Q = 201.46$, $p = 0.000$) and very high ($I^2 = 98.51\%$). For the "nebulizer" subgroup, the effect size of the intervention is large: $SMD = -1.00$ (95% CI: -1.51, -0.50) in favor of the intervention in a statistically significant way. Statistical heterogeneity is significant ($Q = 22.24$, $p = 0.000$) and high ($I^2 = 77.52\%$) (see Appendix).

Fragrance

Based on the type of fragrance used, studies that addressed pain were assigned to the subgroup "other fragrances" ($N = 549$) or "lavender" ($N = 1245$). For the first subgroup, the effect size of the intervention is moderate: $SMD = -0.61$ (95% CI: -1.52, 0.30) in favor of the intervention in a statistically insignificant way. Statistical heterogeneity is significant ($Q = 177.04$, $p = 0.000$) and very high ($I^2 = 95.48\%$). For the second subgroup, the effect size of the intervention is large: $SMD = -1.38$ (95% CI: -1.95, -0.81) in favor of the intervention in a statistically significant way. Statistical heterogeneity is significant ($Q = 336.87$, $p = 0.000$) and very high ($I^2 = 94.95\%$) (see Appendix).

Sensitivity analysis

To assess the robustness of the overall effect of the intervention on pain, the meta-analysis was regenerated by excluding quasi-randomized studies. Considering only randomized studies ($N = 941$), the effect size of the intervention is large: $SMD = -1.12$ (95% CI: $-1.58, -0.66$) in favor of the intervention in a statistically significant way. Statistical heterogeneity is significant ($Q = 154.15, p = 0.000$) and very high ($I^2 = 90.27\%$) (see Appendix).

Publication bias

Publication bias cannot be excluded (Figure 4). In fact, by implementing the Trim and Fill method on the studies that included pain among the outcomes, five studies were cut, and the two effect sizes, the estimated one (in black) and the observed one (in white), do not coincide. Furthermore, both the Egger test ($p = 0.028$) and the Begg and Mazumdar test ($p = 0.009$) are statistically significant.

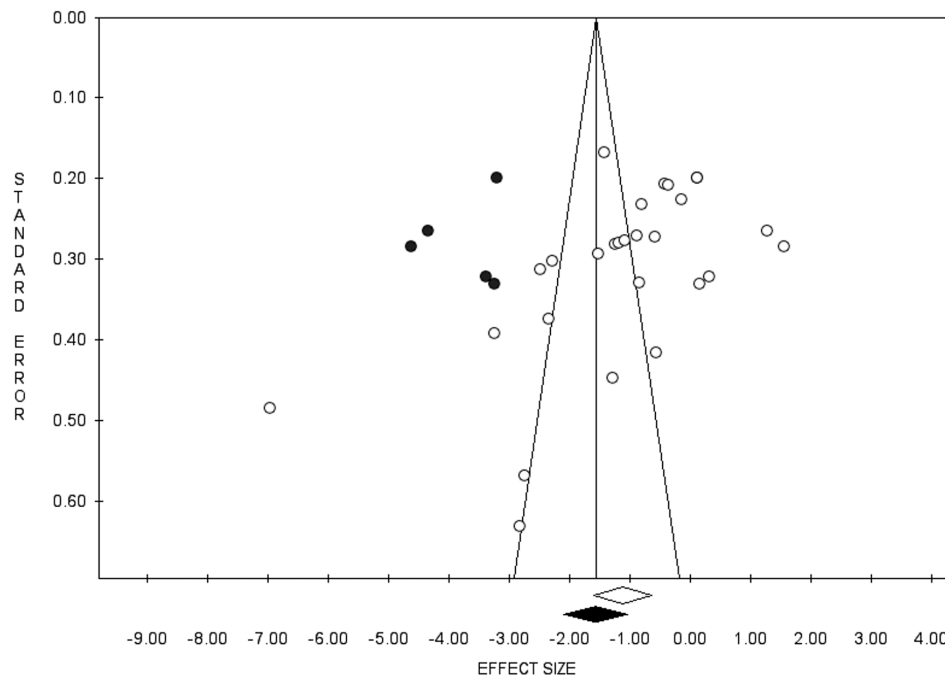


Figure 4. Funnel plot.

Summary of findings

The summary of findings table, carried out in compliance with the GRADE method to evaluate the effect of aromatherapy compared to control on children to be subjected to medical procedures of diagnosis and treatment, produced a very low

certainty/quality of evidence on pain, anxiety, and sleep duration. This is because the evidence was downgraded once because most of the studies presented some concerns or a high risk of bias, once for inconsistency due to substantial heterogeneity, and once for the risk of publication bias (Table 5).

Summary of findings. Effectiveness of aromatherapy for children.					
Aromatherapy compared to control					
Patient or population: children (0 to 18 years) undergoing diagnostic and treatment procedures					
Setting: any					
Intervention: aromatherapy					
Comparison: standard of care, placebo					
Outcome	Anticipated absolute effects* (95% CI)		N° of participants (studies)	Certainty/quality of the evidence (GRADE)	Comments**
	Risk with control	Risk with aromatherapy			
Pain	-	The mean level of pain (SMD) with aromatherapy was 1.12 standard deviations lower (1.60 to 0.65 lower).	1794 (22)	⊕⊕⊕⊕ Very low ^{a,b,c}	This result equates to a big difference in favor of aromatherapy.
Anxiety	-	The mean level of anxiety (SMD) with aromatherapy was 1.08 standard deviations lower (1.52 to 0.64 lower).	856 (9)	⊕⊕⊕⊕ Very low ^{a,b,c}	This result equates to a big difference in favor of aromatherapy.
Sleep duration	-	The mean sleep duration (SMD) with aromatherapy was 0.95 standard deviations lower (1.94 lower to 0.03 higher).	330 (4)	⊕⊕⊕⊕ Very low ^{a,b,c}	There is no evidence of an effect of aromatherapy.
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).					
**0.2 represents a small difference, 0.5 a moderate difference, and 0.8 a large difference.					
CI: confidence interval; SMD: standardized mean difference; qRCTs: quasi-randomized controlled trials; RCTs: randomized controlled trials					
GRADE Working Group grades of evidence					
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect					
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different					
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect					
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					
^a Downgraded once for serious study limitations: trials had some concerns/high risk of bias.					
^b Downgraded once for inconsistency due to substantial heterogeneity (60% < I ² < 90%).					
^c Downgraded once for risk of publication bias.					

Table 5. Summary of findings.

Discussion

The study aimed to evaluate the effect of aromatherapy compared to standard care or placebo on pain, anxiety, sleep duration, and stress in children undergoing diagnostic and therapeutic treatments. In light of the results, the intervention seems positive and with a large effect size on pain, anxiety, and sleep duration. However, the low quality of the studies, the high statistical heterogeneity, and the risk of publication bias determine a very low level of certainty/quality of evidence for all three outcomes; consequently, very little confidence should be placed in the estimate of the observed effect: it is likely that the real effect is substantially different. With regard to physiological signs of stress, aromatherapy seems to have a

statistically significant effect (a) on the reduction of crying duration, heart rate, systolic and diastolic blood pressure, and respiratory rate; (b) on the increase in the percentage saturation of oxygen in the blood; and (c) on the reduction of the level of salivary cortisol. Additional analyses, performed on studies that addressed pain, showed that the benefit of aromatherapy (a) decreased as children grew older (SMD = -2.14, SMD = -1.46, SMD = -1.00 for the age groups 0-2 years, 3-5 years, 6-12 years respectively); (b) was similar in effect size between dental and non-dental procedures; (c) was greater with massage (SMD = -1.55) than with inhalation (SMD = -1.09) or nebulization (SMD = -1.00); and (d) was greater with lavender essential oil (SMD = -1.38) than with other fragrances (SMD = -0.61). The robustness of the overall effect of the intervention on pain was confirmed after excluding quasi-

randomized studies; in fact, considering only randomized studies, the standardized mean difference is equal to $SMD = -1.12$ in favor of the intervention, a value identical to that calculated by also including quasi-randomized studies.

Comparison with the literature

The only systematic review that addressed the effectiveness of aromatherapy in pediatrics^[36] found inconclusive evidence on pain and anxiety; however, the comparison is not very meaningful as the authors did not perform a meta-analysis, included both primary and secondary studies that involved the delivery of the intervention via inhalation, and excluded those that subjected children to dental treatments.

Implications for practice

It is crucial to remember that aromatherapy can be considered a complementary intervention and not a substitute for established effective treatments for the management of pain, anxiety, sleep disorders and stress in children. The results obtained from the meta-analyses are comforting but do not allow a conclusive judgment on the effectiveness of aromatherapy for the management of pain, anxiety, sleep duration, and stress in children undergoing diagnostic and treatment procedures. Although a positive effect of the intervention has been found, the very low quality/certainty of the evidence does not warrant its routine use in daily clinical practice and precludes the production of definitive recommendations. Furthermore, although the studies were conducted in 10 countries spread across four continents, 70% of them were carried out in Asia. This is consistent with the traditional use of herbal medicine in Asian countries; the social and cultural context may have made children in these countries more receptive to aromatherapy and more likely to believe in its benefits^[100]; this may have interfered with the acceptability and effectiveness of the intervention^[32]. In addition, expectations and beliefs about complementary therapies in general depend on cultural sensitivity to the topic. Consequently, it is currently not possible to generalize the effect of aromatherapy to socially and culturally very different realities such as Europe or the United States.

Aromatherapy seems less effective on older children; perhaps active distraction strategies (e.g., video games) may be preferable for them.

Compared to aromatherapy by inhalation or nebulisation, aromatherapy by massage seems more effective^{[101][102]}, although not all opinions in the literature are in agreement^[103]. The application of diluted essential oils to the skin by massage determines absorption and a systematic action; the effect of the fragrance on other patients is minimized, and the oil is delivered to the individual. This last aspect is the core of nursing care^[104]. It is still a matter of discussion whether the observed results are attributable exclusively to aromatherapy or to the effect of the synergy between massage and aromatherapy: in fact, the effectiveness of massage could be greater than that of aromatherapy^[100]^[103]. Touch is an important way to create bonds, communicate

emotions, and decrease the sense of loneliness^[105]; during the massage, the body is touched, and this feeling of care probably contributes to alleviating some symptoms^[103]. Direct inhalation of the fragrance seems more effective than delivery via nebulizer; this is in agreement with literature data^{[68][104]}, in relation to the faster absorption of volatile compounds. Regardless of the delivery method, the therapeutic efficacy of aromatherapy is maximal at the first application, but if administered for a prolonged period of time or for several sessions, it seems to decrease, probably because the olfactory receptors become less sensitive to the aroma^{[103][104][105]}.

An important factor that influences the effect of aromatherapy is the type of essential oil used. The analysis of the included studies highlighted the wide and effective use of lavender oil for its analgesic and anti-inflammatory properties and for the fact that it is one of the safest essential oils^[106].

Despite the positive results, it cannot be excluded that the attention paid to participants and effective communication may have established a climate of trust that favored the benefit of the intervention^[103]. Furthermore, it is possible that the fragrance simply masked unpleasant odors (e.g., disinfectants, antiseptics) typical of a clinical setting and that this effect in itself was therapeutic^[107].

No adverse effects were observed following the intervention in the few studies that have dealt with it^{[49][68][70][72]}.

An unsolved issue, even after performing additional subgroup analyses, is the high statistical heterogeneity between studies. The sources of this heterogeneity may be partly due to chance but above all reflect methodological differences in the recruitment of participants and in the conduct of the studies: (a) children are distributed over a wide age range and therefore are at different stages of neurocognitive development, are in good general health or affected by a serious disease; (b) children are subjected to very different diagnostic and treatment procedures, resulting in different characteristics of pain, anxiety, or stress in terms of, for example, intensity and duration^{[108][109]}; (c) there is a wide heterogeneity of settings (from the community to pediatric intensive care); (d) the exclusion criteria are not homogeneous; (e) the type and degree of parent-child interaction during the procedure and the application of the intervention are not described; (f) the characteristics of the intervention (fragrance used, delivery method, duration, number of sessions) differ; (g) in most studies, aromatherapy was the only intervention, but in some, it was associated with a minimal intervention whose net effect was not evaluated; (h) the control group in some studies received a placebo, and in others, standard care: the placebos are very different from each other (e.g., distilled water or a carrier oil) and the standard care is not described; (i) a wide variety of assessment tools with very different psychometric properties were used to evaluate the primary outcomes.

Implications for research

Despite the growing interest in pediatric aromatherapy in the literature, better quality, well-designed, larger, and possibly

multicenter studies are needed. Furthermore, gender studies on the effect of the intervention are lacking.

Greater effectiveness of aromatherapy could be achieved by developing research aimed at regulating the methods of delivery by inhalation (e.g., nebulization device, volume of the room in which to diffuse the fragrance, duration and number of sessions, type of aromatic oil) or by aromatherapy massage (number and duration of treatments, optimal massage techniques, parts of the body to be massaged, type of essential oils to be mixed in the carrier oil, type of carrier oil). There is also a need for future research to focus on the cost of the intervention, the availability of essential oils, and the potential need for training of health care personnel. Focused studies are needed on testing aromatherapy protocols in selected pediatric units in order to assess the feasibility of widespread implementation.

Finally, further research is needed focusing on the safety of the intervention: the studies that have dealt with reporting any adverse events have been a minority, and although these have not detected any, it cannot be deduced that aromatherapy is risk-free. Safety is a particularly important concern for children, given their high risk of inadvertent exposure and toxicity, and essential oils should be handled as potential poisons and stored out of their reach^[31].

Limitations

Aromatherapy is an intervention for which blinding of participants and caregivers is very difficult; this may have

overestimated the benefit of the intervention. The main problems identified in the studies include the small size of the studies, the choice of an appropriate control group to ensure that participants and caregivers were blinded to group assignment, the placebo effect, the poor reporting of the concentration of constituents in the essential oils used, and the comparability of different interventions.

The mechanisms of action of essential oils are still unclear, and the optimal dosage and duration of exposure to achieve maximum therapeutic effect are poorly studied. Furthermore, the dosage unit cannot be measured precisely as the droplet size depends on the type of essential oil and the dropper used. Generally, subjects could not choose the fragrance; however, children differ greatly from adults in their individual preferences for odors, which may be a function of temperament, age, and neurocognitive development.

Conclusions

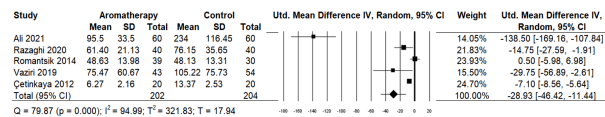
Due to the very low certainty/quality of evidence, at the current state of research it is not possible to make a conclusive assessment of the effect of aromatherapy on pain, anxiety, sleep duration, and stress in children undergoing diagnostic and therapeutic procedures.

Appendix

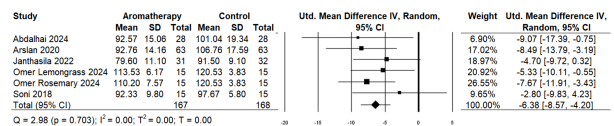
Search strategy.

Resource	Search string	Filter
Cochrane Library	(aromatherapy):ti AND (children):ti	RCT
PubMed	(aromatherapy [ti]) AND (children [ti])	RCT
EMBASE	'aromatherapy':ti AND children:ti	'randomized controlled trial'/de
CINAHL	TI aromatherapy AND TI children	RCT
PsycINFO	aromatherapy.m_titl. AND children.m_titl.	-
Web of Science	aromatherapy (Title) AND children (Title)	-
Scopus	TITLE (aromatherapy) AND TITLE (children)	-
Google Scholar	allintitle: aromatherapy children	-
ClinicalTrials.gov	Aromatherapy	Child (birth – 17) Interventional studies Studies with results

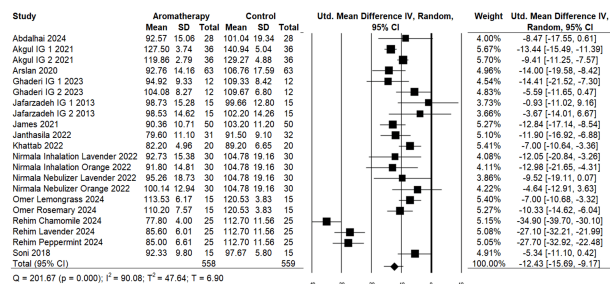
Crying duration: aromathearpy vs. control



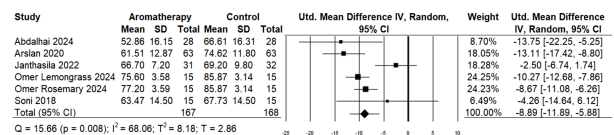
Systolic arterial pressure: aromatherapy vs. control



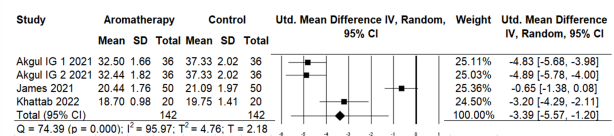
Heart rate: aromatherapy vs. control



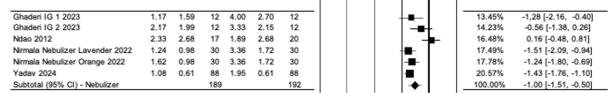
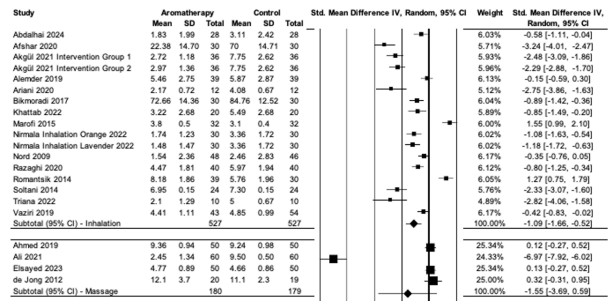
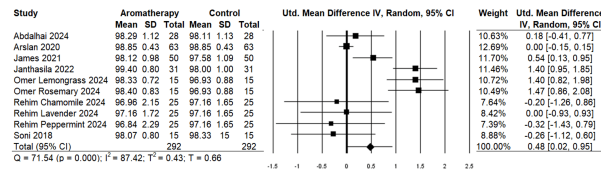
Diastolic arterial pressure: aromatherapy vs. control



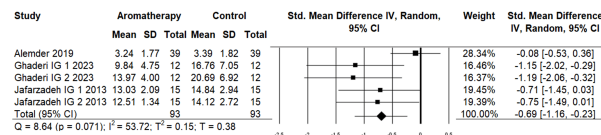
Respiratory rate: aromatherapy vs. control.



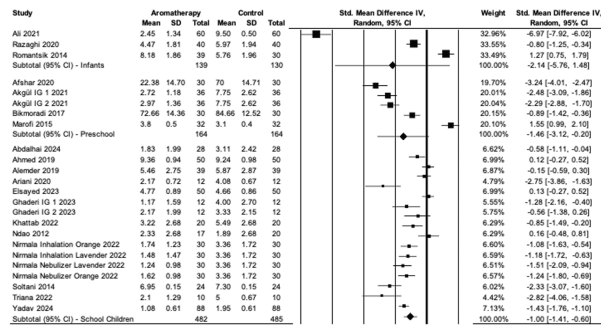
Pain as a function of delivery mode: aromatherapy vs. control



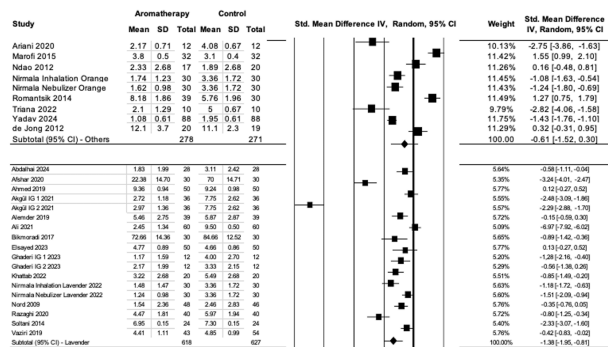
Salivary cortisol level: aromatherapy vs. control



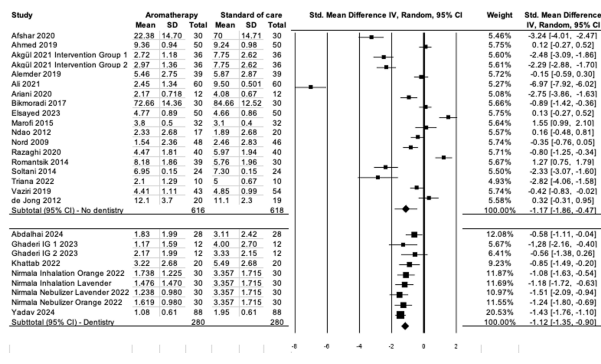
Pain by age: aromatherapy vs. control



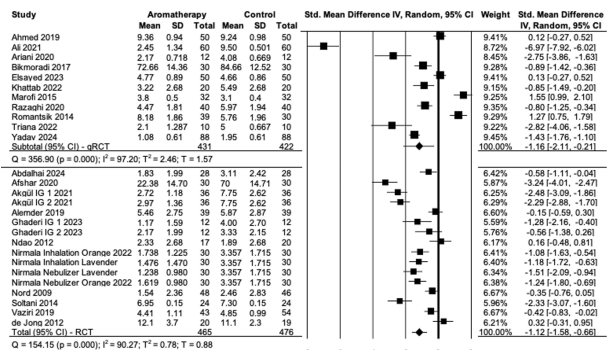
Pain as a function of fragrance type: aromatherapy vs. control



Pain as a function of procedure: aromatherapy vs. control



Sensitivity analysis



Statements and Declarations

Authors' contributions

- Luca Giuseppe Re conceived, designed, and managed the study development process until its conclusion.

- Vincenza Aloia and Stefania Celeste Rippa selected the records after reading the title and abstract.
- Chiara Cartabia and Valentina Tommasi analyzed and evaluated the full texts of the eligible documents for relevance.
- Camilla Ripari, Sara Marotta, and Barbara Bassola extracted the data and information useful for composing the tables illustrating the main characteristics of the included studies.
- Luca Giuseppe Re and Massimiliano D'Elia carried out the methodological quality assessment of the randomized controlled clinical trials with the RoB 2 tool.
- Massimiliano D'Elia and Barbara Bassola carried out the methodological quality assessment of the quasi-randomized controlled clinical trials with the ROBINS-I tool.
- Luca Giuseppe Re performed the statistical analyses and drafted the manuscript text.
- Camilla Ripari drafted the tables and figures.
- Sara Marotta critically revised the manuscript for important intellectual content.

All authors have read and approved the final manuscript.

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