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The Effects of Aroma on Apnea Attacks and Oxygen Saturation Among Preterm Infants: A Systematic Review and Meta-Analysis

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Abstract

Researchers and clinicians need to be aware of procedures that are more adaptable to new and different environments in premature infants; therefore, it is important to conduct a comprehensive review of the effect of aromatherapy on apnea attacks and oxygen saturation (SpO_2) in premature newborns. In this review, databases such as PubMed, Scopus, Web of Science, and Cochrane Library were systematically searched without language and time limitations up to November 1, 2022. Initially, 153 studies were founded, and after duplicate removal, title as well as full-text review, seven studies were enrolled in the final analysis. Studies indicated that aromatherapy with Rosa damascena, vanilla, and breast milk odors could significantly reduce apneas in preterm infants and improve SpO_2 levels. Hence, aromatherapy could consider as an effective adjuvant treatment for the reduction of apnea attacks among preterm infants.
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Keywords: Premature; Aromatherapy; Herbal; Infants; Oxygen Saturation

Introduction

Providing suitable environmental conditions, especially in high-risk groups, including children, women, the elderly [1-4], and patients with life-threatening diseases, is one of the most important duties of the medical team [5-10]. Meanwhile, premature infants and their mothers are among the most critical groups receiving medical care [1-3]. Premature labor (before 37 weeks of gestation) increases the probability of fatality and morbidity due to respiratory immaturity [11]. Apnea–a brief pause for more than 20 seconds–is one of the most prevalent complications experienced by premature infants admitted to the neonatal intensive care unit [12]. In other words, apnea, pallor, bradycardia, and

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cyanosis [13] are reported in approximately 85% of infants with a gestational age equal to or less than 34 weeks [14].
Also, apnea could lead to brain damage, hypotonia, hypotension, neurological disorders, hydrocephalus, and even mortality [15].
The recurrent apnea and the need for mechanical ventilation within the first week of treatment could be decreased using methylxanthines, such as aminophylline, theophylline, and caffeine [14, 16, 17].
However, they cannot completely prevent apnea sequels, and additionally, several undesirable side effects such as hyperactivity, irritability, sleep disorders, tachycardia, and urinary disorders have been noticed in treated infants [18]. As a natural treatment, aromatherapy uses aromatic essential oils extracted from various parts of plants, such as leaves, bark, fruits, stems, seeds, roots, and flowers [19].
The olfactory and gustatory receptors develop by the eighth week of gestation and become functional by the 24th and 17th weeks, respectively [20]. Several studies showed the effects of aromatherapy with vanilla [11, 15, 19, 21], *Rosa damascena* [18], and breast milk odor [13-15] on apnea attacks and oxygen saturation (SpO_2).
Hence, this study aimed to provide evidence through a systematic review of the effects of aromatherapy on apnea attacks and SpO_2 in preterm infants.

Materials and Methods

Search Strategies
This systematic review was conducted according to the PRISMA 2020 Checklist [22]. A comprehensive literature search was conducted in PubMed, EMBASE (via OVID SP), Scopus, and Web of Science until November 2022. We used the medical subject heading (MESH) and free text words for our search in different combinations, such as ((Preterm OR (Premature) AND (Odor OR Olfactory OR Aroma OR aromatherapy OR Smell OR odor) AND (Apnea OR oxygen saturation OR Spo_2). Search strategies were modified as necessary for each specific database. The full search strategies for each database are presented in Table-1.
All the articles found throughout our search process were imported into Endnote X6 (Thomson Reuters, Philadelphia, PA, USA), and duplicates were removed. The titles and abstracts of identified studies were scrutinized for eligibility by four reviewers (SR, MGH, SP, and SFMM) in two groups independently, and full-text versions of selected studies were collected for further assessment.
Four reviewers in two different groups independently examined the full texts, and relevant articles were identified. The discrepancies were examined and finalized by the corresponding author (MM). Also, for better coverage, reference lists of selected articles and review papers were manually searched to identify relevant articles.

Eligibility Criteria and Study Selection
We included all clinical trials that exanimated the impact of aromatherapy on SpO_2 and apnea attacks among preterm infants (less than 37 weeks of gestation).
Also, non-clinical trials, non-human studies, reviews, letters to the editor, multi-sensorial interventions, conference papers, and non-published data were excluded.

Data Extractions
After selecting the relevant studies, data, including first author name, year of publication, type of control, intervention interval, and aroma dosage were entered in a pre-developed form.

Quality Assessments
We used the modified Jadad tool, a checklist that evaluated clinical trial studies [9]. Briefly, Jadad consists of eight questions in five domains (e.i., description of randomization, methods used to generate the sequence of randomization, blinding, method of blinding, description of withdrawals, and dropouts) that scored separately.
The maximum score obtained from the Jadad is equal to eight. Accordingly, studies were categorized into three groups low-(score<4), moderate- (score 4 to 6), and high- (score≥6) quality.
Two authors (SR and MM) independently performed the quality assessment, and a consensus was made in the case of disagreement.

Table 1. The Search Strategies In the Different Databases

Database	Search statement
PubMed	(((((“Infant, Premature”[Mesh] AND “Infant, Extremely Premature”[Mesh]) AND (“Infant, Premature/blood”[Mesh] OR “Infant, Premature/cerebrospinal fluid”[Mesh] OR “Infant, Premature/growth and development”[Mesh] OR “Infant, Premature/immunology”[Mesh] OR “Infant, Premature/metabolism”[Mesh] OR “Infant, Premature/physiology”[Mesh] OR “Infant, Premature/psychology”[Mesh] OR “Infant, Premature/urine”[Mesh])) AND (“Infant, Extremely Premature/blood”[Mesh] OR “Infant, Extremely Premature/cerebrospinal fluid”[Mesh] OR “Infant, Extremely Premature/growth and development”[Mesh] OR “Infant, Extremely Premature/immunology”[Mesh] OR “Infant, Extremely Premature/metabolism”[Mesh] OR “Infant, Extremely Premature/physiology”[Mesh] OR “Infant, Extremely Premature/psychology”[Mesh] OR “Infant, Extremely Premature/urine”[Mesh])) AND (“Aromatherapy/adverse effects”[Mesh] OR “Aromatherapy/classification”[Mesh] OR “Aromatherapy/economics”[Mesh] OR “Aromatherapy/ethics”[Mesh] OR “Aromatherapy/history”[Mesh] OR “Aromatherapy/instrumentation”[Mesh] OR “Aromatherapy/methods”[Mesh] OR “Aromatherapy/mortality”[Mesh] OR “Aromatherapy/nursing”[Mesh] OR “Aromatherapy/psychology”[Mesh] OR “Aromatherapy/standards”[Mesh] OR “Aromatherapy/statistics and numerical data”[Mesh] OR “Aromatherapy/trends”[Mesh] OR “Aromatherapy/veterinary”[Mesh])) AND (“Odorants/analysis”[Mesh] OR “Odorants/legislation and jurisprudence”[Mesh] OR “Odorants/prevention and control”[Mesh])) AND “Agnosia”[Majr]
Web of Science	TI= (Infant * OR “Infant, Premature”) AND TI=(“Bariatric Surgery” OR “Preterm Infant” OR “Premature Newborn” OR “Preterm Neonate” OR “ Prematurity “) AND TI=(“Aromatherapy*” OR “ Odor “ OR Smell *) AND TI=(“ Olfactometer *” OR “ Olfactory stimulation*”)
Scopus	(TITLE-ABS (Infant *) OR TITLE-ABS (“Infant, Premature “)) AND (TITLE-ABS(“Preterm Infant”) OR TITLE-ABS(“Preterm Newborn “) OR TITLE-ABS(“Premature Newborn “) OR TITLE-ABS(Premature Neonate) OR TITLE-ABS(“Preterm Neonate “)) AND (TITLE-ABS(Prematurity *) OR TITLE-ABS(“Aromatherapy “) OR TITLE-ABS(Odor) OR TITLE-ABS(Smell *)) AND (TITLE-ABS(Olfactometer *) OR TITLE-ABS(Olfactory stimulation *))
Cochrane Library	Title Abstract Keyword Premature infant AND Title Abstract Keyword Prematurity AND Title Abstract Keyword odour AND Title Abstract Keyword Olfactory stimulation AND Title Abstract Keyword Preterm infant AND Title Abstract Keyword odor AND Title Abstract Keyword Olfactometer AND Title Abstract Keyword smell Title Abstract Keyword Premature infant OR Title Abstract Keyword Prematurity OR Title Abstract Keyword odour OR Title Abstract Keyword Olfactory stimulation OR Title Abstract Keyword Preterm infant OR Title Abstract Keyword odor OR Title Abstract Keyword Olfactometer OR Title Abstract Keyword smell
Embase	(‘Preterm infant’:ab,ti OR ‘Premature infant’:ab,ti OR ‘Preterm Newborn’:ab,ti OR ‘Premature Newborn’:ab,ti OR ‘ Premature Neonate’:ab,ti OR ‘Preterm Neonate’:ab,ti OR ‘Premature baby’:ab,ti OR ‘Preterm baby’:ab,ti OR ‘ Preterm infant, Aromatherapy’:ab,ti OR ‘ Preterm infant; Aroma’:ab,ti OR ‘ Preterm infant, Smell ‘:ab,ti AND ‘Aromatherapy’:ab,ti OR ‘Aroma’:ab,ti OR ‘Smell’:ab,ti OR ‘Odor’:ab,ti OR ‘odour’:ab,ti OR ‘Olfactometer’:ab,ti OR ‘Olfactory stimulation’:ab,ti)

Statistical Analysis

The heterogeneity of studies was evaluated by the Chi-squared and I^2 tests.

The results were reported using a random-effects model, and the standardized mean difference (SMD) method was applied to the intergroup comparisons at a 95% confidence interval (CI). Also, the "Metaprop" command was used to perform meta-analyses of proportions on STATA14 (Stata, College Station, TX, USA).

Results

1. Characteristics of Studies

Our initial search identified 153 articles, and after duplicate removal, as well as the title and abstract screening, 13 articles were chosen for full-text review. Finally, seven studies [11, 15, 19, 21, 23-25] were included in our review (Figure-1).

The characteristics of included studies are presented in Table-2. Totally, 463 preterm infants were evaluated. Aromatherapy with vanilla, R. damascena, and breast milk odor was performed in four [11, 15, 19, 21], one [25], and four [11, 19, 23, 24] studies, respectively. The Jadad score for included studies are shown in Table-3.

2. Effect of Aromatherapy On Apnea Attacks

2.1. Vanilla

Although four studies [11, 15, 19, 21] assessed the effect of aromatherapy with vanilla, only three studies [15, 19, 21] indicated the role of vanilla on the frequency of apnea attacks (Table-2).

Edraki *et al*. [15] showed that receiving vanilla solution (2%) could significantly reduce apnea attacks compared to the control group (Table-2).

Also, Kanbur *et al*. [19] reported a significant decrease in the frequency of apnea in preterm neonates in the vanilla group compared to the breast milk and control groups.

In Yaghoubi *et al*. study [21], the frequency of apnea attacks changed after treatment with cotton impregnated with 2ml of vanilla extract compared to the control group (P=0.016, Table-2).

2.2. R. damascena

In a study by Aghagoli *et al*. [25], the number of apnea attacks was significantly lowered in the *R. damascena* group than in control (P<0.05, Table-2).

3. Effect of Aromatherapy On SpO_2

Overall, the SMD of SpO_2 between the aromatherapy and the control group was -0.48 (95%CI: -0.708 to -0.25, I^2=28.1%), which indicates significant differences (P<0.001, Figure-2).

3.1. Vanilla

Regarding Figure-3, the SpO_2 levels of the vanilla group were significantly different compared to the control group (SMD: -0.43, 95%CI: -0.72 to -0.14, P=0.003; Figure-3).

In Yaghoubi *et al*. study [21], a significant difference was observed in SpO_2 levels of premature neonates with apnea between the vanilla group and the control (Table-2). Also, Edraki *et al*. [15] reported a significant difference in SpO_2 between the vanilla group and the control group (P=0.02, Table-2). In contrast, Neshat *et al*. [11] showed no significant differences among preterm infants of vanilla and control groups regarding SpO_2 (Table-2).

3.2. R. damascena

In the study of Aghagoli *et al*. [25], decreased SpO_2 level was significantly (P<0.05) improved in the 10% *R. damascena* group than in control (distilled water) among preterm infants with apnea (Table-2).

3.3. Breast Milk

The SpO_2 levels between breast milk and the control groups were significantly different (SMD=-0.38, 95%CI: -0.66 to -0.105, P=0.007, Figure-4)

Park *et al*. [23] demonstrated no significant differences in SpO_2 levels between the milk odor and control groups (P=0.548, Table-2). Also, Alemdar *et al*. [24] indicated that the mean level of SpO_2 was not significantly different in breast milk odor groups compared to mother voice and control groups (Table-2).

However, Neshat *et al*. [11] stated that the breast milk odor group could significantly improve the SpO_2 of premature infants compared to the control group (P=0.014, Table-2).

Table 2. Characteristics of Included Studies

Authors [Ref]	Location	Groups	Dose/Interval	Outcome(s)
Neshat *et al*. [11]	Iran	-Vanilla (n=45) -Breast milk (n=45) -Control (n=45)	-Ten drops vanilla/five minutes before and 30 seconds after sampling	Improvement SpO_2 in the breast milk odor group (P=0.014); however, no significant change in the vanilla group (P=0.16) in comparison with the control
Edraki *et al*. [15]	Iran	-Vanilla (n=18) -Control (n=18)	Solution 2%/every 12 hours	A significant difference between the vanilla group and control regarding SpO_2 and apnea
Kanbur *et al*. [19]	Turkey	-Breast milk (n=13) -Vanilla (n=16) -Control (n=13)	Not mentioned	A significant decrease in the frequency of apnea in the vanilla group compared to the breast milk and controls
Yaghoubi *et al*. [21]	Iran	-Vanilla (n=19) -Control (n=18)	A piece impregnated with 2ml in approximately 20 cm from infants/ every 12 hours	The frequency of apnea attacks and SpO_2 level changed after treatment in vanilla extract (P=0.016) compared with the control groups
Park *et al*. [23]	Korea	-Breast milk (n=14) -Control (n=16)	A 2cc was placed 10 cm away from the infants/ eight times per day for three days	Significant differences in SpO_2 levels between the milk odor and control group
Alemdar *et al*. [24]	Turkey	-Breast milk (n=30) -Mother voice (n=30) -Cover (n=31) -Control (n=32)	Solution placed on gauze sponge 15 min before Peripheral cannulation. And up to 15 min after the procedure. .	The breast milk odor groups were not different from the mother voice and control group in terms of mean SpO_2
Aghagoli *et al*. [25]	Iran	-*R. damascena* (n=30) -Control (n=30)	Two drops/every three hours for three days	The number of apnea attacks and SpO_2 levels was significantly lower in the *R. damascena* group than in the control

Table 3. The Quality of Included Studies Based on Jadad

Questions	Edraki *et al.*	Kanbur *et al.*	Yaghoubi *et al.*	Neshat *et al.*	Park *et al.*	Alemdar *et al.*	Aghagoli *et al.*
Was the study descript as randomized?	1	0	0	1	1	0	1
Were the methods of randomization appropriate?	1	1	1	1	1	1	1
Was the study descript as blinded?	1	0	1	1	0	0	1
Was the methods of blinding appropriate?	0	1	0	0	1	0	0
Was a description of withdrawals and dropouts?	0	0	1	1	1	0	0
Was a clear description of inclusion and exclusion criteria	1	1	0	1	0	1	0
Was the method used to assess the adverse effects described?	1	1	1	0	0	1	1
Was the method of statistical analysis described?	1	1	1	1	1	1	1
Total score	6	5	5	6	5	4	5

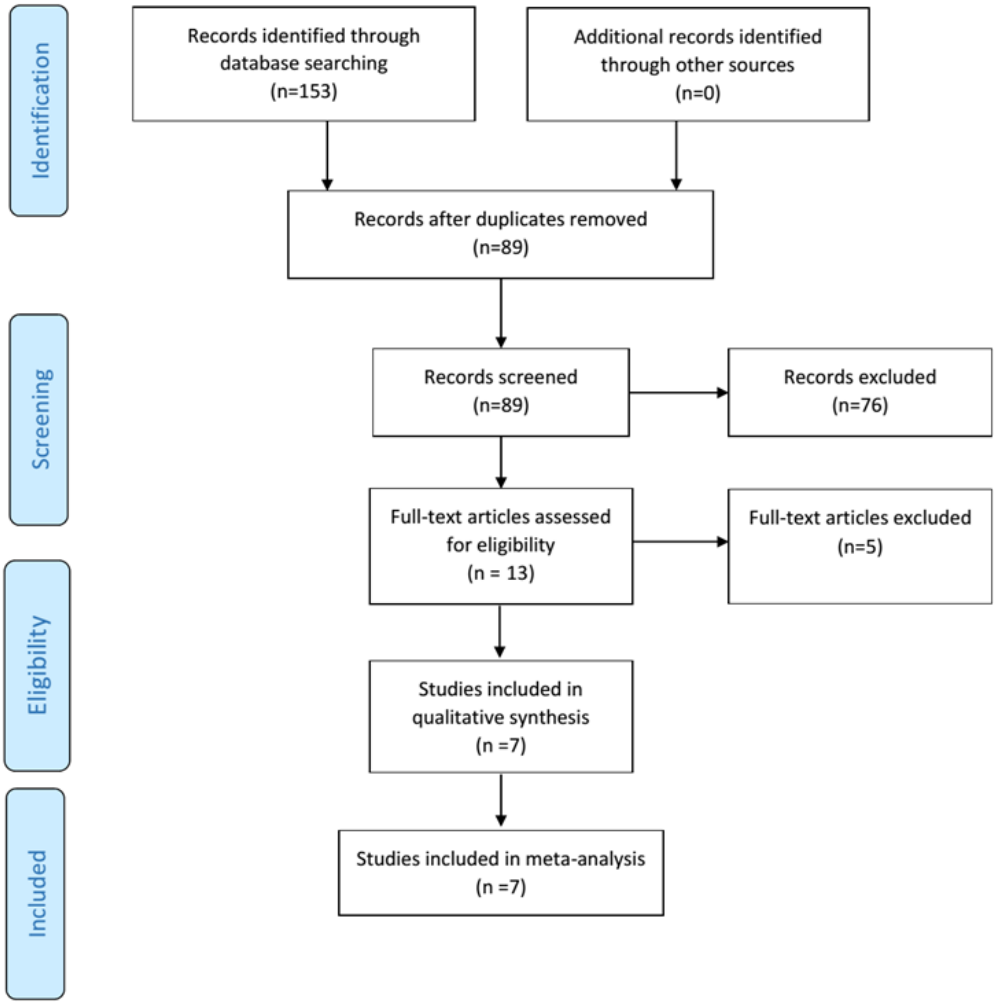

Figure 1. PRISMA flowchart of the study.

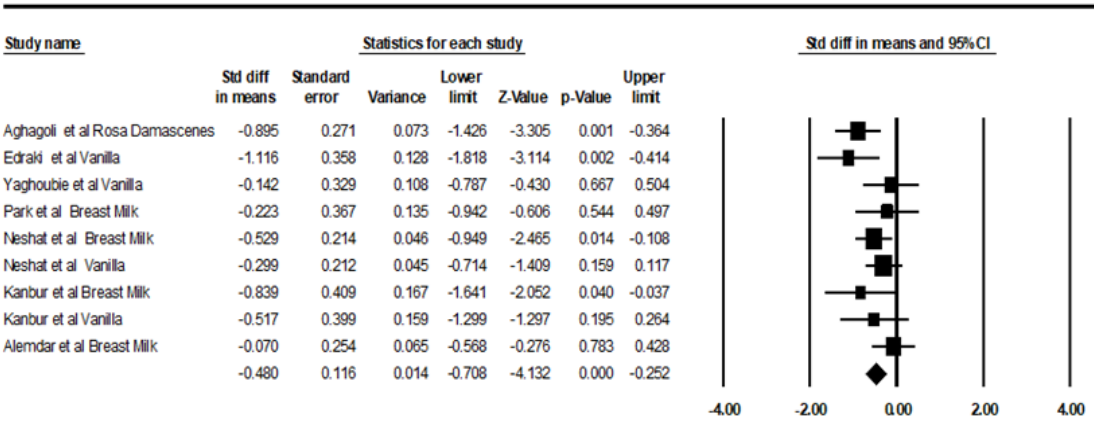

Figure 2. The effects of aromatherapy on SpO_2. The horizontal lines denote the 95% CI; ■ point estimate (square size corresponds to its weight); ♦ combined overall effect of treatment.

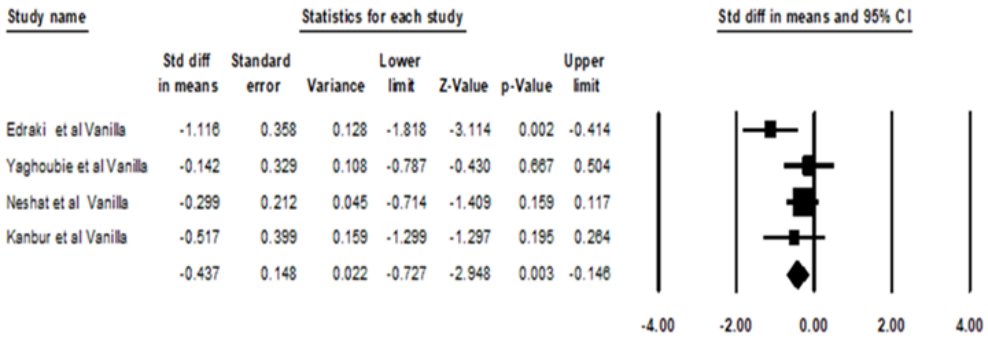

Figure 3. The effects of aromatherapy with vanilla. The horizontal lines denote the 95% CI; ■ point estimate (size of the square corresponds to its weight); ♦ combined overall effect of treatment.

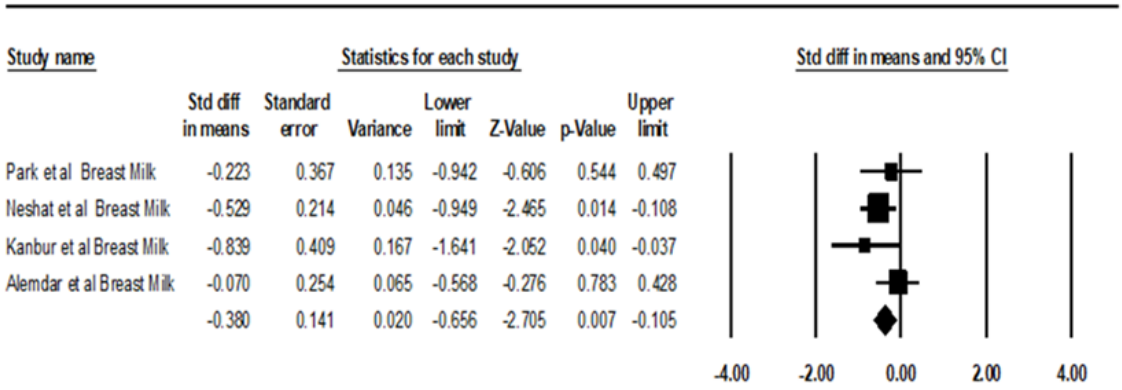

Figure 4. The effects of aromatherapy with breast milk odor on SpO_2. The horizontal lines denote the 95% CI; ■ point estimate (size of the square corresponds to its weight); ♦ combined overall effect of treatment.

Discussion

The current systematic review found that aromatherapy had both preventive [15] and therapeutic effects [18] on apneas in preterm infants. Ataei Nakhaei *et al*. [26] in a systematic review, revealed that aromatherapy effectively treats apnea in preterm infants. However, the authors reiterated that their findings should be interpreted cautiously due to the small sample size and the low number of studies [26]. Evidence indicated that vanilla could impact on apnea in some ways. Indeed, vanilla could be absorbed via the nasal mucosa and enter the brain through the bloodstream and improve orbitofrontal blood flow [15]. Also, vanilla helps newborns deal with stress and directly affects the respiratory centers [18]. Hence, it balances psychological and physiological states [18].

Aromatherapy with the *R. damascena* could be applied as an effective intervention for premature infants suffering from apnea, followed by routine therapy to reduce bradycardia and improve SpO_2 levels [25]. The extract of *R. damascena* contains christin and kaempferol, which has some beneficial effects on the nervous system [27] and reduces pain [28]. Moreover, the hydro-alcoholic extract of *R. damascena* has a dilatory effect on respiratory airways [25, 28]; hence, it could reduce anxiety as well as improve sleep quality, especially in premature infants hospitalized due to apnea [29-31].

Although the current study involved more studies compared to previous research [26], there were some limitations. Indeed, the studies included in our systematic review had a small sample size, and only one type of apnea (i.e., the idiopathic apnea of prematurity) was evaluated. Hence, further investigations to verify the effectiveness of this non-pharmacological method in various types of apnea are recommended.

Conclusion

Aromatherapy with natural substances (e.g., *R. damascena*) and even artificial ones can be used as an additional treatment to improve the breathing condition of premature infants with apnea.

Conflict of Interest

Authors declare there were no any conflicts of interest.

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