Review Paper

# Investigating the Effect of Olfactory Stimulation in Preterm Infants: A Review Study

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## ABSTRACT

**Background:** Besides respiratory problems, the lack of or inefficient oral feeding performance is a major problem facing premature newborns. Researchers and clinicians need to be aware of procedures and positive olfactory stimuli mediating major problems and more adaptable premature infants to the neonatal intensive care unit and hospital environments. Accordingly, it is essential to undertake a comprehensive review of the effect of olfactory stimulation in preterm infants.

**Objectives:** This study aims to assesses the effect of aromatherapy on apnea, the transition from tube feeding (gavage) to oral feeding, pain, growth and duration of hospital stay.

**Methods:** The major English databases, such as PubMed, Embase, Scopus, Cochrane Library and ISI Web of Science, were systematically reviewed without any time restrictions up to April 12, 2022. Two researchers assessed articles, and any discrepancies were resolved by a third author. The data were extracted through a pre-prepared. The 5-item Jadad scale was used to assess the quality of the articles found in the search.

**Results:** A total of 13 studies were included in the current review. There are controversial results about the aromatherapy effect of pleasant odor vanillin on apnea attacks in preterm infants. Rosa damascenes odor had a therapeutic effect on apnea attacks, but not breast milk odor. The breast milk and the vanillin odor were effective in preterm infants' venipuncture. Meanwhile, hospital discharge time and transition time from tube feeding to oral feeding were shorter; however, the results were insignificant.

**Conclusions:** Olfactory stimulation by some pleasant odors is a safe, non-invasive and family-friendly intervention and can help improve apnea attacks and painful procedures in preterm infants. There was no clear effect of exposure to pleasant odor on hospital discharge and transition time from tube feeding to oral feeding.

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## Introduction

Premature birth, described as under 37 weeks of gestation, increases the likelihood of fatality and morbidity due to respiratory immaturity and ineffectual oral feeding performance [1]. In the neonatal intensive care unit, premature infants are frequently exposed to painful procedures during the first days [1, 2]. Also, infants are exposed to several negative olfactory stimuli including strong perfumes or scented aftershave, alcohol, cleaning chemicals, alcohol-based hand rubs, and oral remedies. These odors must be curtailed with a positive stimulus, such as breastfeeding-related substances as well as materials with parental smell utilized as a counterbalance [3]. The olfactory and gustatory receptors develop by the eighth week of gestation and become functional by the 24$^{th}$ and 17$^{th}$ weeks, respectively [4]. According to several studies, olfactory stimulation could alleviate pain and neonatal crying during painful procedures by releasing fragrances and other familiar aromas, such as the mother's milk and amniotic odor [5], can mark a sooner transition from the feeding tube to efficient oral feeding [6], mediates the apnea.

Besides respiratory problems, the lack of or inefficient oral feeding performance is a major problem facing premature newborns [6]. Researchers and clinicians need to be cognizant of procedures and positive olfactory stimuli mediating major problems and more adaptable premature infants to the neonatal intensive care unit and hospital environments. Accordingly, it is essential to undertake a comprehensive review of the effect of aromatherapy on apnea, the transition from tube feeding (gavage) to oral feeding, pain, growth, and duration of hospital stay.

## Methods

The major English databases, such as PubMed, Embase, Scopus, Cochrane Library and Web of Science, were systematically reviewed without any time restrictions up to April 12, 2022. The search keywords were as follows: ([Preterm infant*] OR [premature infant*] OR [preterm newborn] OR [premature newborn] OR [premature neonate*] OR [preterm neonate*] OR [premature baby] OR [preterm baby] OR (prematurity]) AND ([aromatherapy] OR [olfactometer] OR [olfactory stimulation] OR [aroma] OR [odor]).

All the clinical trials assessed the effect of the aroma on variables, such as apnea, the transition from tube feeding (gavage) to oral feeding, pain, growth, and duration of hospital stay.

### Inclusion and exclusion criteria

All clinical trials that investigated the effect of the aroma on variables such as apnea, transition time to oral feeding, pain, growth, and duration of hospital stay in preterm infants were included in the study. Preterm infants were considered birth less than 37 weeks of gestational age. Only interventions that used olfactory sense were included in the study. Non-English articles, letters to the editor, reviews, non-human studies and multi-sensorial intervention studies were excluded. Two researchers independently evaluated study eligibility. Disagreements were resolved by consensus, which required the reviewers to discuss the reasoning for their decisions.

### Data extraction

Data extraction was done independently by two of the authors using pre-piloted forms. The accuracy of the data was subsequently adjudicated by a third reviewer. The Table 1 list the considered parameters, including the first author, the year of publication, the location and type of study, gestational age and infant weight at birth. Other characteristics of subjects were Apgar score, hemoglobin, stability or instability of neonate, intervention and control groups, aroma dose, intervention intervals, aroma distance from the infant's nose, and outcomes.

### Quality assessment

The Jaded scale is a validated scale and was used to assess the risk of bias in the study. The quality of studies was evaluated according to the Jaded scale. It consisted of 8 items, as shown in Table 2. The methodological quality of the studies was assessed independently by the two authors. Disagreements between the assessors were subsequently adjudicated by a third reviewer (Table 2).

## Results

A total of 927 titles were retrieved from a main database search. In addition, none of the trials were identified by hand-searched of the bibliographies of relevant articles. After removing duplicates, 347 trials remained of which 312 studies that were excluded because they did not meet the inclusion criteria based on title and abstract. The full text of the remaining 35 studies was reviewed, and another 22 studies were excluded because they did not meet the inclusion criteria. Finally, 13 studies were included in the review (Figure 1).

**Table 1.** Extracted data from the articles

| Study (y) | Location | Design | Gestational Age and Weight | Intervention | Control | Dose Interval Distance | No. in Analysis (Intervention/ Control) | Outcome |
|---|---|---|---|---|---|---|---|---|
| Kanbur & Balci 2019 [7] | Turkey | RCT | 28-35 w | 1) Vanilla (n=16); 2) Breast milk (n=16) | Control (nothing; n=16) | Vanilla extract or breast milk (15 drops)/every 6 h | 16/13/13 | The frequency of apnea decreased significantly (P=0.001) in preterm infants in the vanilla (1.68) group compared to the breast milk (4.07) and control (4.46) |
| Edraki et al. 2013 [8] | Iran | RCT | <36 w <2500 g | Vanillin solution (n=18) | Nothing (n=18) | Vanillin extract (2 mL)/every 12 h | 18/18 | The number of episodes of apnea decreased (3.1-fold) significantly in the vanilla group than in the no treatment (t=8.32, P<0.05) |
| Yaghoubi et al. 2017 [9] | Iran | RCT | <32 w <2000 g | Vanilla (n=20) | Distilled water (n=20) | Vanillin extract (2 mL)/every 12 h | 19/18 | No significant improvement between vanillin and control groups in the number of apnea attacks (P=0.142). |
| Aghagoli et al. 2016 [5] | Iran | RCT | 29-33 w 900-1500 g | *R. damascena* distillate (n=30) | Distilled water (n=30) | Two drops of *R. damascena* 10%; every 3 h for three days | 30/30 | The number of apnea attacks was significantly lower in the rosa damascenes group (0.47±0.13) compared to the control (2.6±0.4) group (P=0.001). |
| Baudesson de Chanville et al. 2017 [10] | France | RCT | 30-37 w | Breast milk (n=16) | Odorless (n=17) | Breast milk odors 6 L/min and manually switched on 3 min before the venipuncture and switched off 9 min after the completionof the procedure (5 min intervals) | 16/17 | A significant decrease was observed in pain profile during venipuncture in neonates receiving their mother's milk odor in comparison with the control (6.3 [interquartile range=5-10] vs 12.0 [interquartile range=7-13], P=0.03) |
| Jebreili et al. 2015 [11] | Iran | RCT | 28-34 w | 1) Vanilla odor (n=45) 2) Breastmilk odor (n=45) | Control (n=45) | Cotton balls 10 cm from the infant's nose; 12 h before sampling | 45/45/45 | A significant difference was observed in pain score during venipuncture (7.3, 9.2, 10.6; P=0.01) and after venipuncture in (6, 8.1, 8.8; P=0.01) among three groups of mother's milk odor, vanilla odor, and control. |
| Badiee et al. 2013 [12] | Iran | RCT | 32-37 w | Breast milk (n=25) | Formula milk (n=25) | 2 mL milk odors (3 min before and up to 9 min after heel prick blood sampling | 25/25 | A significant decrease in score after heel lancing venipuncture in neonates receiving their mother's milk odor in comparison with the control (5.4 compared to 9 with P<0.001). |
| Wu et al. 2020 [13] | Taiwan | RCT | Infants born preterm | Routine care (n=36); (condition 2) BM-OT (n=33); (condition 3) BM-OT+HBs (n=33); or (condition 4) BM-OT+HBs+NNS (n=36) | Routine care (n=36) | A cotton ball, which the intervener placed around the infant's nose until the tenth min of recovery | 36/33/33 | Mean pain scores were significantly lower in preterm infants exposed to three conditions than in controls during peripheral venipuncture procedures. |

| Study (y) | Location | Design | Gestational Age and Weight | Intervention | Control | Dose Interval Distance | No. in Analysis (Intervention/ Control) | Outcome |
|---|---|---|---|---|---|---|---|---|
| Bellieni et al. 2001 [14] | Italy | RCT | 28–35 w of gestational age | Oral glucose plus sucking (C); SS: see below (D); oral water (E); oral glucose without sucking | A) Control condition | Baby oil (babygella, Guieu labs) | 75 | Sensorial saturation has a greater analgesic effect on heel prick in preterm infants in comparison with control and sucking+oral glucose groups (P<0.001). |
| Beker et al. 2017 [4] | Australia | RCT | <29 w | Smell and taste of milk (n=28) | No exposure to the smell and taste of milk (n=23) | A drop of milk (50–100 µL) | 28/23 | Differences between the two groups were non-significant (P=0.1) in the transition from tube feeding to oral feeding. |
| Khodagholi et al. 2018 [15] | Iran | RCT | 28-32 w mini-mum=1000 g | NNS+breast milk odor (n=16) NNS | NNS+pad without breast milk odor (n=16) | 5 min of gavage, three times per day for 10 days; cotton pads around 2-3 cm near the infant's nose | 16/16 | The difference between the two groups was non-significant transition time oral feeding (100% vs 81; P=0.07). |
| Schriever et al. 2018 [16] | Ger-many | RCT | >27 w | 1) Rose (not food-associated; n=50) 2) Vanilla odor (food-associated; n=50) | Odorless probe (n=50) | Sniffing sticks 10 s before each feeding by bottle or by nasogastric tube but not before breastfeeding; 2 cm under the nostrils | 46/49/40 | The difference in vanilla odor (8±5.4) and control group 15±7.3 between two groups was significant but the difference between rose odor (12±6.6) and control (15±7.3) was not significant in transition time to oral feeding. |
| Cao Van H. 2017 [6] | Belgium | RCT | Mean=34 w Mean=2200 g | Cinnamon (n=12) +anise (n=13) | Nothing (n=25) | Scented pen under the nose of the child for 10 s before each meal, regardless of the feeding modality odorless pen for the control group | 25/24 | The length of hospital stay tended to be shorter in cinnamon (n=12) +anise group compare to the control (P=0.12; confidence interval (95% CI, −1.0%, 7.7%) |

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Abbreviations: RCT: Randomized controlled trial; W: Week; BM: Breast milk; NNS: Not-nutritive sucking; HBs: Heartbeat sounds.

### The effect of aromatherapy on apnea

Studies assessed the effect of aromatherapy with vanilla, breast milk, and Rosa damascenes on apnea. Two studies assessed the effect of aromatherapy with vanilla on apnea. The frequency of apnea decreased significantly in preterm infants in the vanilla group than in the breast milk and control [7] and no treatment (P<0.05) [8]. In contrast in Yaghoubi et al.'s study, the number of apnea attacks did not change after treatment with Vanilla control (P=0.142) [9]. In the study by Aghagoli et al. (2016) the number of apnea attacks was significantly lower in the Rosa damascenes group than control (distilled water) (P<0.05) [5].

### The effect of aromatherapy on painful procedures

Three studies showed a significant decrease in premature infant pain profile score after heel lancing during venipuncture and after venipuncture in neonates receiving their mother's milk odor in comparison with the control [10-12].

According to Wu et al. (2020) mean pain scores were significantly lower in preterm infants exposed to breast milk odor (n=36) or heartbeat sounds (HBs) + BM odor (n=33) or BM odor + non-nutritive sucking (NNS) + HBs (n=36) compared to the controls (routine care; n=36) during peripheral venipuncture procedures [13]. One study assessed the effect of sensorial saturation (SS) on

**Table 2.** The quality of the studies according to the jaded scale

| Author's (y) | Randomization Mention | Random Sequence Generation | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Description of Withdrawals and Dropouts | Clear Description of the Inclusion and Exclusion Criteria | Description of the Method Used to Assess Adverse Effects | The Method of Statistical Analysis |
|---|---|---|---|---|---|---|---|---|
| Kanbur & Balci, 2019 [7] | + | + | _ | _ | + | + | - | + |
| Edraki et al. 2013 [8] | + | + | - | + | + | + | - | + |
| Yaghoubi et al. 2017 [9] | + | - | - | + | + | + | - | + |
| Aghagoli et al. 2016 [5] | + | - | - | + | + | + | - | + |
| Baudesson de Chanville et al. 2017 [10] | + | + | - | + | + | + | - | + |
| Jebreili et al. 2015 [11] | + | + | - | + | + | + | - | + |
| Badiee et al. 2013 [12] | + | - | + | + | - | + | - | + |
| Wu et al. 2020 [13] | + | + | - | + | + | + | - | + |
| Bellieni et al. 2001 [14] | + | + | - | + | + | + | - | + |
| Beker et al. 2017 [4] | + | - | + | + | + | + | - | + |
| Khodagholi et al. 2018 [15] | + | - | + | + | + | + | - | + |
| Schriever et al. 2018 [16] | + | - | - | - | + | | | |
| Cao Van 2017 [6] | + | + | - | + | + | + | - | + |

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painful procedures preterm infants were randomized into five different procedures: control, 10% oral glucose plus sucking, SS, oral water, and 10% oral glucose. SS is a multisensorial stimulation consisting of delicate tactile, vestibular, gustative, olfactory, auditory, and visual stimuli. SS has a greater analgesic effect on heel prick in preterm infants in comparison with control and sucking + oral glucose groups (P<0.001) [14].

### Aromatherapy on transition from tube feeding (gavage) to oral feeding

Two studies assessed the effect of breast milk odor and one study assessed the effect of vanilla odor or rose on transition from tube feeding to oral feeding. In Beker et al.'s study, preterm infants were exposed to either the smell or taste of milk before each feed reached full enteral feeds at a shorter time (13.5 days) than no exposure group (15.5 days); however, the difference between the two groups was non-significant (P=0.1) [4]. In Khodagholi et al., study, milk odor in combination with NNS compared to alone NNS decreased transition feeding time to oral feeding (P=0.07) [15]. In Schriever et al.'s study, infants preterm exposed to the vanilla odor than the control group indicated a faster transition from tube feeding to oral feeding but, the difference was not significant between rose odor and control [16].

### Aromatherapy on hospital discharge

In Cao Van et al.'s study [6], the length of hospitalization was shorter in infants stimulated with anise or cinnamon (group A) than odorless stimulation (control group). However, it was non-significant (P=0.12). In Khodagholi et al, milk odor in combination with NNS compared to NNS alone decreased hospital discharge time(P=0.07) [15].

## Discussion

According to this review, olfactory stimulation by some pleasant odors was effective on painful procedures and apnea attacks in preterm infants. Meanwhile, hospital discharge time and transition time from tube feeding to oral feeding were shorter. However, the results were insignificant.

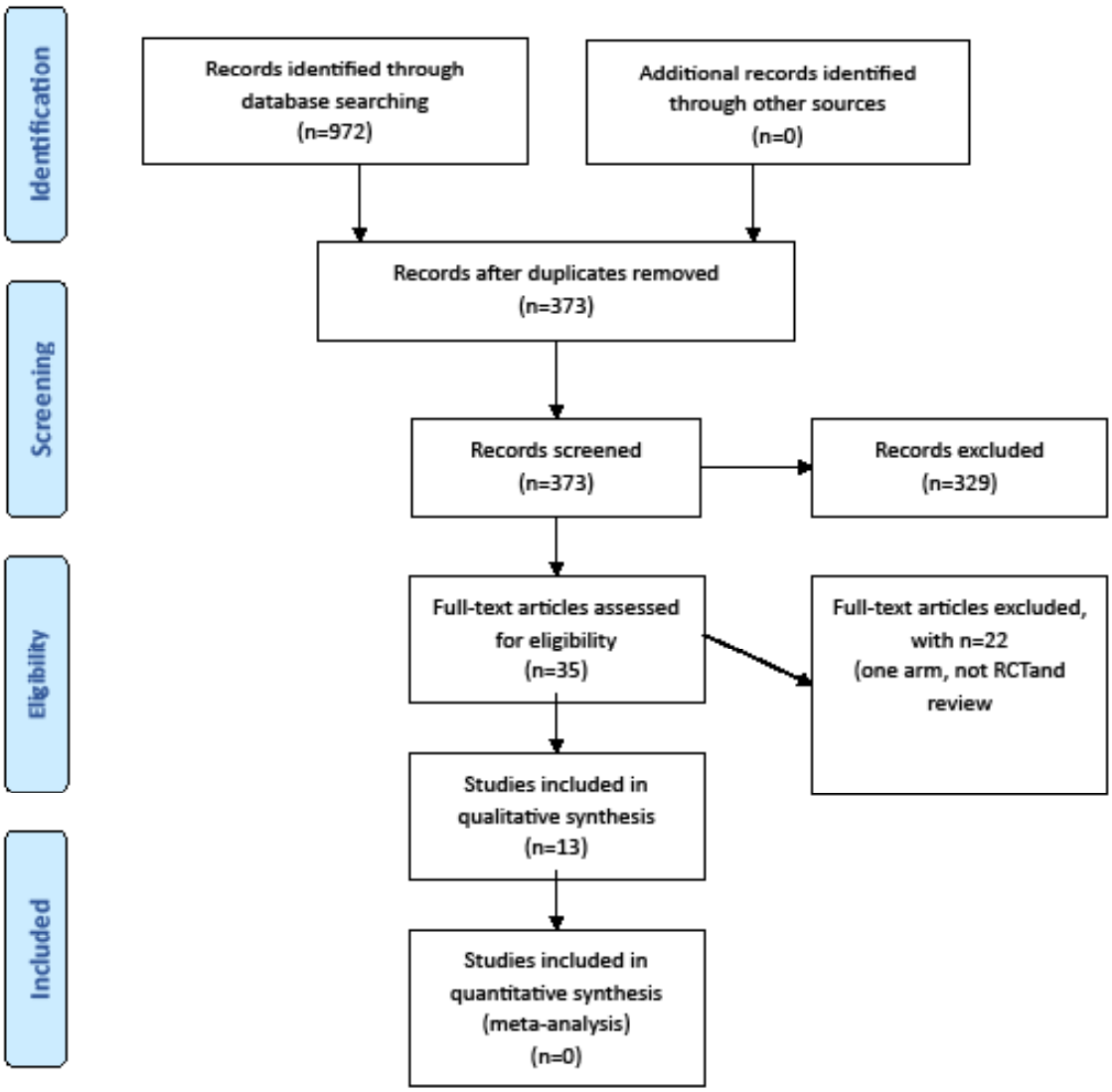


**Figure 1.** PRISMA 2009 flow diagram

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This review found that there are controversial results about the aromatherapy effect of pleasant odor vanillin on apnea attacks in preterm infants [8]. Rosa damascenes odor had a therapeutic effect on apnea attacks [23], but not other odors [5]. Recently, two systematic reviews reported consistent results with significant effects on apnea attacks in preterm infants. The first systematic review with three studies has shown that aromatherapy is effective in treating apnea in preterm infants. However, due to the small sample size and low number of studies included in their systematic review, the authors reiterated that their findings should be interpreted with caution [17]. The second systematic review and meta-analysis showed that the treatment with aromatherapy can significantly decrease apnea attacks compared to the control in the preterm infant [18]. According to our research aromatherapy with vanillin has a preventing [9] and therapeutic effect [7] on apneas episodes in preterm infants. In addition, regarding the multidimensional effect of vanillin, first, it may run through the nasal mucosa and enroll in the brain through the bloodstream. Second, the vanillin can improve orbitofrontal blood flow. Third, vanillin helps the newborns deal with the stress [8]. Fourth, vanillin probably has pharmacological properties; therefore, it can directly and indirectly affect the respiratory centers. In a study, the number of apnea attacks was significantly lower in the *R. damascenes* group compared to the control (distilled water; $P<0.05$) [5]. The extract of *R. damascena* stimulates axons and dendrites in the nervous system [19]. Moreover, the hydro-alcoholic extract of *R. damascenes* has a dilatory effect on respiratory airways [5, 20].

According to our review, BM and the vanillin odor were effective in preterm infants' venipuncture [3, 4, 13] that is consistent with previous systematic reviews addressing the effect of pleasant odor on painful procedures. A systematic review showed aromatherapy with lavender could decrease painful procedures in infants and children [21]. A meta-analysis with eight randomized controlled trials involving 453 participants conducted by Zhang in 2018 showed that BM odor significantly decreased pain scores in newborns with large effect sizes for painful procedures [22]. Another systematic review was published by Norouziasl et al. and concluded that aromatherapy with the mother's milk, vanilla and the mother's odor could lessen painful procedures and improve physiological parameters [23].

According to a study, aromatherapy with anise or cinnamon led to a sudden transition from the feeding tube to effectual oral feeding in premature infants [6]. Moreover, cinnamon contains expressive anti-allergic, anti-ulcerogenic, antipyretic, anesthetic, and analgesic characteristics. It also has medicinal applications due to its strong aromatic, sweet, and warm odor or food additives [24]. The anise essential oil boosts the production of BM, expedites milk secretion, and acts as a diuretic substance. The anise seeds consist of anethole, which is a debilitated estrogenic agent. Given its role as a dopamine receptor antagonist, it could be activated by prolactin secretion increment [25].

However, published clinical studies reported controversial results about this effect, According to our study, infants exposed to milk odor transitioned from tube feeding to oral feeding 2-10 days earlier. However, the results were insignificant. The results of a systematic review of two studies revealed that exposure to the smell and taste of milk with gastric or nasogastric tube feedings had no clear effect on the time to reach full sucking feeds and full tube feeding [26]. Findings of a meta-analysis with 8 studies revealed that in comparison to the control group, infants preterm exposed to either pleasant odors or BM odor transitioned from tube feeding to oral feeding earlier [27]. Smell and taste play a significant role in improving digestion and absorption of food. Therefore, providing some milk for the infant to smell and taste via an orogastric or nasogastric tube can potentially bolster their ability to tolerate greater volumes of milk quickly.

The results of our review of three studies concluded there was no evidence of a clear effect of exposure to pleasant odors such as anise cinnamon or milk odor on hospital discharge time and weight at discharge in preterm infants. Inconsistent with our results, a systematic review of two studies revealed exposure to the smell and taste of milk with an orogastric or nasogastric tube may decrease the length of hospitalization in preterm infants [26].

## Conclusion

Olfactory stimulation by some pleasant odors can help improve apnea attacks in preterm infants. Olfactory stimulation by milk odor is a safe, non-invasive and family-friendly intervention in improving painful procedures in preterm infants. The results were not conclusive although it was found that infants preterm exposed to pleasant odors had a shorter transition time from tube feeding to oral feeding and discharge earlier in the day.

### Limitations and suggestions for future studies

This study faced some limitations of this study. First of all, the studies included in our systematic review had a small sample size. Second, only one kind of apnea, i.e. the idiopathic apnea of prematurity, has been studied in newborns. Hence, it is required to conduct further investigation to verify the effectiveness of this non-pharmacological method in various types of apnea. Despite randomization, the gender distribution was not balanced. Hence, it was obvious that male gender exhibited a higher disadvantage in premature infants. A review of literature male and female infants respond differentially to environmental stimuli, with different growth and neurodevelopmental trajectories. No study included in our review assessed sexually dimorphic response to aromatherapy on painful producers. Future studies should be conducted as systematic reviews with meta-analyses on this topic to address the gaps in knowledge identified from the results of this review.

## Ethical Considerations

### Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

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This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

## Authors contributions

Conceptualization, project administration, and funding acquisition: Masumeh Ghazanfarpour, Mohammad Hasan Mohammadi, and Hashem Lashgari Kalat; Methodology: Zahra Ramazanian Bafghi, Shahabaddin Sorouri, Hossein Ali Kharazmi, Najmeh Soltani Nejad, Mohammad Hasan Mohammadi and Hashem Lashgari Kalat; Software: Hashem Lashgari Kalat, Masumeh Ghazanfarpour and Shahabaddin Sorouri; Validation and supervision: Shahabaddin Sorouri, Hossein Ali Kharazmi, Hashem Lashgari Kalat and Mohammad Hasan Mohammadi; Formal analysis: Zahra Ramazanian Bafghi, Najmeh Soltani Nejad and Masumeh Ghazanfarpour; Investigation: Hashem Lashgari Kalat, Masumeh Ghazanfarpour and Mohammad Hasan Mohammadi; Resources: Shahabaddin Sorouri, Hossein Ali Kharazmi, Najmeh Soltani Nejad and Hashem Lashgari Kalat; Data curation: Shahabaddin Sorouri, Hossein Ali Kharazmi, Mohammad Hasan Mohammadi and Hashem Lashgari Kalat; Writing the original draft: Hashem Lashgari Kalat, Shahabaddin Sorouri, Hossein Ali Kharazmi and Mohammad Hasan Mohammadi; Review and editing: All authors.

## Conflicts of interest

The authors declared no conflict of interest.

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