# Review Paper

# Effects of *Purgative Manna* on the Serum Bilirubin Level of Newborns: A Systematic Review and Meta-analysis

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## ABSTRACT

**Background:** The rate of neonatal jaundice is increasing. Due to the complications associated with phototherapy, researchers have consistently sought alternative methods, including herbal remedies.

**Objectives:** In this study, we conduct a systematic review and meta-analysis to investigate the impact of *Purgative manna* consumption on the serum bilirubin levels of neonates.

**Methods:** In this systematic review and meta-analysis, we conducted an online search on various databases, including Barakat Gostar, scientific information database (SID), Magiran, IranDoc, PubMed, Scopus, Web of Science, Cochrane and the Google Scholar search engine, without time restrictions, up to July 20, 2023. Data analysis was performed using the STATA software, version 14. Meanwhile, the significance level was considered $P<0.05$.

**Results:** We examined 12 clinical trial articles, involving a total of 1557 neonates. Before the intervention, there was no statistically significant difference in the bilirubin levels of neonates between the two groups (standardized mean difference [SMD]=-0.02; 95% confidence interval [CI], -0.12%, 0.09%; P=0.473). After *Cotoneaster* consumption, the serum bilirubin levels of the intervention group decreased (SMD=-3.50; 95% CI, -5.76%, -1.24%; P=0.000). Following phototherapy, the bilirubin levels of the control group also decreased (SMD=-2.14; 95% CI, -4.01%, -0.27%; P=0.000). After the intervention, at 12 h (SMD=-0.45; 95% CI, -0.80%, -0.10%; P=0.000), 24 h (SMD=-0.63; 95% CI, -1%, -0.26%; P=0.000), 36 h (SMD=-0.95; 95% CI, -1.69%, -0.20%; P=0.000), 48 h (SMD=-0.62; 95% CI, -0.92%, -0.31%; P=0.000), and 72 h (SMD=-0.84; 95% CI, -1.40%, -0.29%; P=0.000) post-intervention, the bilirubin levels of neonates in the *Cotoneaster* group were lower compared to the control group.

**Conclusions:** *Cotoneaster* consumption is more effective than phototherapy alone in reducing the bilirubin levels of neonates.

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## Introduction

The majority of newborns experience jaundice in the early stages of their lives [1]. The incidence of neonatal jaundice and the associated healthcare costs are increasing worldwide [2].

Phototherapy is the most common intervention for the prevention and treatment of severe hyperbilirubinemia [3]. However, many infants require blood transfusions if phototherapy fails to reduce serum bilirubin levels effectively [4]. On the other hand, retinal degeneration, diarrhea, dehydration, skin rashes [5], and oxidative stress-related diseases such as necrotizing enterocolitis and patent ductus arteriosus (PDA) are among the side effects of phototherapy [6]. In China, infants exposed to phototherapy for hyperbilirubinemia receive combined treatment with traditional Chinese herbal medicines, which have been shown to reduce serum bilirubin levels and improve jaundice [7].

Accordingly, the development of traditional and complementary medicine for neonatal jaundice is an important and potentially safe step in primary healthcare [8, 9]. Before phototherapy became commonplace, complementary medicine, such as *Cotoneaster* was used in Iran to treat neonatal jaundice [10]. *Cotoneaster*, or *Purgative manna*, is a white and slightly yellowish, sweet substance derived from the plant genus *Cotoneaster* spp. which belongs to the Rosaceae family. Its most important compounds include carbohydrates, such as mannitol, fructose, glucose, and sucrose, which induce osmotic diarrhea and may thus contribute to a reduction in bilirubin levels [11].

Numerous studies have examined the effects of *P. manna* on neonatal jaundice. A systematic review and meta-analysis demonstrated that Manna could reduce the duration of phototherapy by decreasing bilirubin levels in jaundiced neonates [12]. A randomized clinical trial compared the use of *P. manna* drops with phototherapy and demonstrated that *P. manna* resulted in a greater reduction in serum bilirubin concentration [13]. Another intervention study found that *Cotoneaster* administration had no significant impact on neonatal jaundice compared to a placebo [14]. Contradictory results from previous studies highlight the necessity for a systematic review and meta-analysis in this area. Accordingly, this study investigates the effect of *Cotoneaster* consumption on serum bilirubin levels in neonates worldwide, with no geographical location restrictions. However, all published studies were conducted in Iran. Since this plant is native to Iran and East Asian countries, it is not utilized in many other countries, and consequently, studies in this regard have not been conducted.

## Materials and Methods

The present research was a systematic review and meta-analysis designed based on the preferred reporting items for systematic reviews and meta-analysis guidelines [15].

### Search strategy

In this meta-analysis, an online search was conducted on Iranian databases, including Barakat Gostar, Scientific Information Database (SID), Magiran, IranDoc and international databases, such as PubMed, Scopus, Web of Science, Cochrane and the Google Scholar search engine, without time restrictions up to July 20, 2023. Language restriction was not performed during the search. The search was performed using standard keywords and MeSH terms, including "*Purgative manna*," "billinaster," "shir-khesht," "*Cotoneaster*," "rosaceae," "jaundice," "icterus," "hyperbilirubinemia," "bilirubinemia," "infant," and "newborn." The keyword combinations were explored using logical operators (AND, OR) within the mentioned databases. For manual searching, a list of eligible primary studies was also examined. A sample of the search strategy in the PubMed database is provided below: ([*Purgative manna* OR billinaster OR shir-khesht OR *Cotoneaster* OR Rosaceae] AND [jaundice OR Icterus OR hyperbilirubinemia OR bilirubinemia]) AND (infant, newborn OR neonatal).

### Population, intervention, comparison, and outcome components

The components of population, intervention, comparison and outcome for this study were as follows: The population included clinical trial studies, involving infants as participants; the intervention comprised an intervention group that could either solely use a *Cotoneaster*-derived product or receive *Cotoneaster* in conjunction with phototherapy; the comparison group could include several scenarios, namely no intervention (one-group, before-after, trial), placebo, or phototherapy; and the outcome of the studies under investigation should assess at least the serum bilirubin level.

### Inclusion criteria

The inclusion criteria for this study were clinical trial studies that evaluated the effect of *P. manna* consumption on infant jaundice.

### Exclusion criteria

The exclusion criteria comprised observational studies, review studies, studies with no access to the full text, protocol papers, conference studies, studies with low quality, studies lacking necessary data for data analysis, and duplicate studies

### Quality assessment of primary studies

After identifying the included studies, two independent reviewers assessed the quality of clinical trials using the Cochrane collaboration's checklist for assessing the risk of bias in randomized trials [16]. This checklist comprises seven questions, each addressing a critical aspect of bias in clinical trials. Each question has three response options, namely high risk of bias, low risk of bias, and unclear. After completing the risk of bias assessment for all studies, discrepancies in responses to the questions in each study were evaluated. Any disagreements were resolved through consensus or agreement between the two assessors, resulting in a unified response.

### Data extraction

Two independent researchers conducted data extraction from the included studies. The extracted data were entered into a checklist that included the following information: First author's name, publication year of the study, total number of infants, number of female and male infants, infant weight, infant age, type of maternal delivery (cesarean or vaginal), study location, *Cotoneaster* dosage, number of infants in the intervention and control groups, and Mean±SD of serum bilirubin levels before and after the intervention in the intervention and control groups. A third researcher reviewed the extracted data from the previous two researchers to resolve any discrepancies.

### Statistical analysis

All included studies had both intervention and control groups and repeatedly measured serum bilirubin levels at baseline and at multiple time points (at regular intervals of 12 h). This allowed for the calculation of within-group mean differences and between-group mean difference indices. The standardized mean difference (SMD) was estimated using the sample size, Mean±SD of serum bilirubin levels before and after the intervention in the intervention and control groups. The SMD indicates the strength of the relationship, with values closer to zero representing a weaker relationship and values closer to one or higher indicating a stronger relationship [17]. To assess heterogeneity, the Cochrane Q test and $I^2$ index were used. Subgroup analysis and meta-regression were used to investigate the sources of heterogeneity, and the Funnel plot was used to assess publication bias [18]. The $I^2$ index has three classifications (<25% indicates low heterogeneity, between 25% and 75% shows moderate heterogeneity and >75% indicates high heterogeneity) [19]. In this study, a random-effects model was used for data analysis. Data analysis was performed using the STATA software, version 14, and the significance level was considered P<0.05.

## Results

### Study selection

In the initial search, a total of 206 articles were found. Upon reviewing the titles of the studies, 49 duplicate studies were removed. The abstracts of the remaining 157 articles were examined, and of these, 24 articles were excluded due to the unavailability of their full texts. Among the remaining 133 articles, 6 were excluded because they lacked the necessary data for data analysis. Out of the remaining 127 articles, an additional 115 articles were excluded based on other exclusion criteria, leaving 12 articles for qualitative evaluation, all of which were of acceptable quality (Figure 1).

### Summary of reviewed studies

In this study, 12 clinical trial articles with a total of 1557 infants (781 infants in the control group and 776 infants in the intervention group) were examined. Out of these, 2 studies investigated the effect of *Cotoneaster* on preventing neonatal jaundice [20, 21], and 10 studies investigated the effect of *Cotoneaster* on the treatment of neonatal jaundice [4, 10, 13, 14, 22–27]. There were no statistically significant differences between the intervention and control groups in terms of the number of participants, age, weight, gender and serum bilirubin levels of the infants. Other information from the reviewed articles is presented in Table 1.

### Analysis of the primary outcome

According to Figure 2, in the intervention group, after the administration of *Cotoneaster*, the serum bilirubin levels of infants significantly decreased (SMD=-3.50; 95% CI, -5.76%, -1.24%; P=0.000).

Figure 3 shows that in the control group, after phototherapy, the serum bilirubin levels of infants signifi-

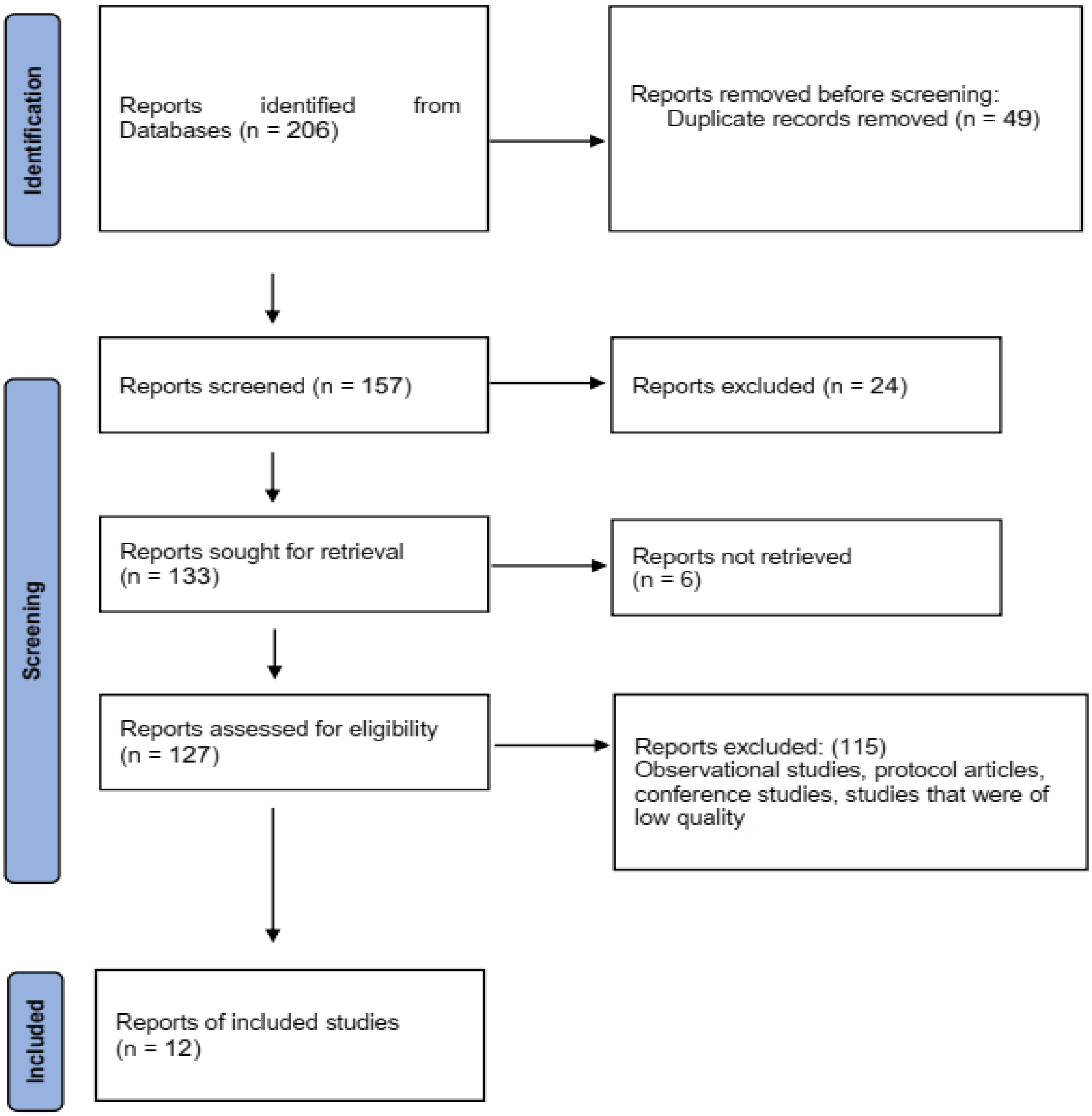


**Figure 1.** Flowchart of entering studies into the systematic review and meta-analysis process

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cantly decreased (SMD=-2.14; 95% CI, -4.01%, -0.27%; P=0.000). Meanwhile, phototherapy is currently the most common method for the treatment of jaundice and the reduction of bilirubin levels in infants.

Before the intervention and in the baseline state, there was no statistically significant difference in serum bilirubin levels between the two groups (intervention and control; SMD=-0.02; 95% CI, -0.12%, 0.09%; P=0.473). This is expected since infants were evaluated upon entry into the study and did not receive any treatment (Figure 4).

Figure 5 demonstrates that infants who received *Cotoneaster* had significantly lower bilirubin levels compared to the control group, which received phototherapy alone (SMD=-0.73; 95% CI, -1.17%, -0.30%; P=0.000).

### Subgroup analysis

In the intervention group, at time intervals of 12 h, 24 h, 36 h, 48 h, 60 h and 96 h after *Cotoneaster* administration, the serum bilirubin levels of infants showed a noticeable reduction, reaching their peak at 96 h after the intervention. However, at 72 h and 84 h after *Cotoneaster* administration, there was no effect on the bilirubin levels of infants.

**Table 1.** Characteristics of studies included in the systematic review and meta-analysis process

| Authors | Type of Study | Prevention or Treatment | Year of Study | City in Iran | Weight (g) | Type of Delivery | Age (d) | Sample Size in Compare Group | Sample Size in Intervention Group | No. | | Dose of *P. manna* | Time (h) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Girls | Boys | | |
| Fakhri et al. 2022 [20] | Single-center double-blinded parallel randomized clinical trial | Treatment | November 2017 to September 2018 | Sari | 2500-4000 | Normal delivery (n=33), Cesarean (n=67) | 2 to 8 | 50 | 50 | 45 | 55 | 1 g/d | 12 |
| Fakhri et al. 2022 [20] | Single-center double-blinded parallel randomized clinical trial | Treatment | November 2017 to September 2018 | Sari | 2500-4000 | Normal delivery (n=33), Cesarean (n=67) | 2 to 8 | 50 | 50 | 45 | 55 | 1 g/d | 24 |
| Fakhri et al. 2022 [20] | Single-center double-blinded parallel randomized clinical trial | Treatment | November 2017 to September 2018 | Sari | 2500-4000 | Normal delivery (n=33), Cesarean (n=67) | 2 to 8 | 50 | 50 | 45 | 55 | 1 g/d | 48 |
| Fakhri et al. 2022 [20] | Single-center double-blinded parallel randomized clinical trial | Treatment | November 2017 to September 2018 | Sari | 2500-4000 | Normal delivery (n=33), Cesarean (n=67) | 2 to 8 | 50 | 50 | 45 | 55 | 1 g/d | 72 |
| Aghababaeian et al. 2021 [21] | Randomized, triple-blind clinical trial | Treatment | From late 2016 to early 2018 | Dezful | 2500-4000 | Normal delivery (n=48), Cesarean (n=48) | 2 to 10 | 48 | 48 | 47 | 49 | 300 mg | 24 |
| Aghababaeian et al. 2021 [21] | Randomized, triple-blind clinical trial | Treatment | From late 2016 to early 2018 | Dezful | 2500-4000 | Normal delivery (n=48), Cesarean (n=48) | 2 to 10 | 48 | 48 | 47 | 49 | 300 mg | 48 |
| Aghababaeian et al. 2021 [21] | Randomized, triple-blind clinical trial | Treatment | From late 2016 to early 2018 | Dezful | 2500-4000 | Normal delivery (n=48), Cesarean (n=48) | 2 to 10 | 48 | 48 | 47 | 49 | 300 mg | 72 |
| Mahyar et al. 2019 [10] | Single-blind randomized controlled clinical trial | Treatment | 2017-2018 | Qazvin | 2500-4000 | Normal delivery (n=17), Cesarean (n=23) | 2 to 10 | 20 | 20 | 16 | 24 | 3 drops/kg | 24 |
| Mahyar et al. 2019 [10] | Single-blind randomized controlled clinical trial | Treatment | 2017-2018 | Qazvin | 2500-4000 | Normal delivery (n=17), Cesarean (n=23) | 2 to 10 | 20 | 20 | 16 | 24 | 3 drops/kg | 48 |

| Authors | Type of Study | Prevention or Treatment | Year of Study | City in Iran | Weight (g) | Type of Delivery | Age (d) | Sample Size in Compare Group | Sample Size in Intervention Group | No. | | Dose of *P. manna* | Time (h) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Girls | Boys | | |
| Monsef et al. 2019 [13] | Randomized double-blind clinical trial | Treatment | 2014 | Hamadan | 2500-4000 | NR | 7.67 | 75 | 75 | NR | NR | 5 drops/kg | 24 |
| Monsef et al. 2019 [13] | Randomized double-blind clinical trial | Treatment | 2014 | Hamadan | 2500-4000 | NR | 7.67 | 75 | 75 | NR | NR | 5 drops/kg | 48 |
| Monsef et al. 2019 [13] | Randomized double-blind clinical trial | Treatment | 2014 | Hamadan | 2500-4000 | NR | 7.67 | 75 | 75 | NR | NR | 5 drops/kg | 72 |
| Monsef et al. 2019 [13] | Randomized double-blind clinical trial | Treatment | 2014 | Hamadan | 2500-4000 | NR | 7.67 | 75 | 75 | NR | NR | 5 drops/kg | 96 |
| Fakhri et al. 2019 [22] | Randomized double-blind controlled clinical trial | Prevention | January 2017 to October 2017 | Sari | 2500-4000 | Normal delivery (n=92), Cesarean (n=353) | 2 to 14 | 223 | 222 | 217 | 228 | 3 drops/kg | 24 |
| Fakhri et al. 2019 [22] | Randomized double-blind controlled clinical trial | Prevention | January 2017 to October 2017 | Sari | 2500-4000 | Normal delivery (n=92), Cesarean (n=353) | 2 to 14 | 223 | 222 | 217 | 228 | 3 drops/kg | 48 |
| Fakhri et al. 2019 [22] | Randomized double-blind controlled clinical trial | Prevention | January 2017 to October 2017 | Sari | 2500-4000 | Normal delivery (n=92), Cesarean (n=353) | 2 to 14 | 223 | 222 | 217 | 228 | 3 drops/kg | 72 |
| Ameli et al. 2017 [23] | Randomized clinical trial | Treatment | June 22, 2015-March 5, 2016 | Mashhad | 3200 | NR | 2 to 14 | 49 | 49 | NR | NR | 5 drops/kg | 12 |
| Ameli et al. 2017 [23] | Randomized clinical trial | Treatment | June 22, 2015-March 5, 2016 | Mashhad | 3200 | NR | 2 to 14 | 49 | 49 | NR | NR | 5 drops/kg | 24 |
| Ameli et al. 2017 [23] | Randomized clinical trial | Treatment | June 22, 2015-March 5, 2016 | Mashhad | 3200 | NR | 2 to 14 | 49 | 49 | NR | NR | 5 drops/kg | 36 |
| Ameli et al. 2017 [23] | Randomized clinical trial | Treatment | June 22, 2015-March 5, 2016 | Mashhad | 3200 | NR | 2 to 14 | 49 | 49 | NR | NR | 5 drops/kg | 48 |
| Rafieian-Kopaei et al. 2016 [24] | Randomized clinical trial | Treatment | 2010 | Shahrekord | 2500-4000 | NR | 2 to 23 | 30 | 30 | NR | NR | 3 drops/kg | 12 |
| Rafieian-Kopaei et al. 2016 [24] | Randomized clinical trial | Treatment | 2010 | Shahrekord | 2500-4000 | NR | 2 to 23 | 30 | 30 | NR | NR | 3 drops/kg | 24 |

| Authors | Type of Study | Prevention or Treatment | Year of Study | City in Iran | Weight (g) | Type of Delivery | Age (d) | Sample Size in Compare Group | Sample Size in Intervention Group | No. | | Dose of *P. manna* | Time (h) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Girls | Boys | | |
| Rafieian-Kopaei et al. 2016 [24] | Randomized clinical trial | Treatment | 2010 | Shahrekord | 2500-4000 | NR | 2 to 23 | 30 | 30 | NR | NR | 3 drops/kg | 36 |
| Rafieian-Kopaei et al. 2016 [24] | Randomized clinical trial | Treatment | 2010 | Shahrekord | 2500-4000 | NR | 2 to 23 | 30 | 30 | NR | NR | 3 drops/kg | 48 |
| Rafieian-Kopaei et al. 2016 [24] | Randomized clinical trial | Treatment | 2010 | Shahrekord | 2500-4000 | NR | 2 to 23 | 30 | 30 | NR | NR | 3 drops/kg | 72 |
| Fallah et al. 2014 [25] | Randomized clinical trial | Treatment | Between September 2012 and February 2013 | Yazd | >2500 | NR | 3 to 7 | 30 | 30 | NR | NR | 5 drops/kg | 24 |
| Fallah et al. 2014 [25] | Randomized clinical trial | Treatment | Between September 2012 and February 2013 | Yazd | >2500 | NR | 3 to 7 | 30 | 30 | NR | NR | 5 drops/kg | 48 |
| Mansouri et al. 2012 [26] | Double-blind clinical trial | Prevention | 2009 | Sanandaj | 3200 | Normal delivery (n=93), Cesarean (n=47) | 3 to 5 | 70 | 70 | 72 | 68 | 5 drops/kg | |
| Ghotbi F, 2006 [4] | Randomized clinical trial | Treatment | 2003-2005 | Tehran | 2500-4000 | Normal delivery (n=42), Cesarean (n=22) | 3 to 11 | 32 | 32 | 30 | 34 | 5 g | 12 |
| Ghotbi et al. 2006 [4] | Randomized clinical trial | Treatment | 2003-2005 | Tehran | 2500-4000 | Normal delivery (n=42), Cesarean (n=22) | 3 to 11 | 32 | 32 | 30 | 34 | 5 g | 24 |
| Ghotbi et al. 2006 [4] | Randomized clinical trial | Treatment | 2003-2005 | Tehran | 2500-4000 | Normal delivery (n=42), Cesarean (n=22) | 3 to 11 | 32 | 32 | 30 | 34 | 5 g | 36 |
| Shahfaraht et al. 2005 [14] | A prospective and double-blind | Treatment | 2002 | Mashhad | >2500 | NR | NR | 54 | 50 | NR | NR | 6 g | 12 |
| Shahfaraht et al. 2005 [14] | A prospective and double-blind | Treatment | 2002 | Mashhad | >2500 | NR | NR | 54 | 50 | NR | NR | 6 g | 24 |
| Shahfaraht et al. 2005 [14] | A prospective and double-blind | Treatment | 2002 | Mashhad | >2500 | NR | NR | 54 | 50 | NR | NR | 6 g | 36 |

| Authors | Type of Study | Prevention or Treatment | Year of Study | City in Iran | Weight (g) | Type of Delivery | Age (d) | Sample Size in Compare Group | Sample Size in Intervention Group | No. | | Dose of *P. manna* | Time (h) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Girls | Boys | | |
| Shah Farhat et al. 2005 [14] | A prospective and double-blind | Treatment | 2002 | Mashhad | >2500 | NR | NR | 54 | 50 | NR | NR | 6 g | 48 |
| Shah Farhat et al. 2005 [14] | A prospective and double-blind | Treatment | 2002 | Mashhad | >2500 | NR | NR | 54 | 50 | NR | NR | 6 g | 60 |
| Azadbakht et al. 2005 [27] | Clinical trial | Treatment | NR | Mazandaran | >=2500 | NR | 3 to 8 | 100 | 100 | NR | NR | 5 drops/kg | 12 |
| Azadbakht et al. 2005 [27] | Clinical trial | Treatment | NR | Mazandaran | >=2500 | NR | 3 to 8 | 100 | 97 | NR | NR | 5 drops/kg | 24 |
| Azadbakht et al. 2005 [27] | Clinical trial | Treatment | NR | Mazandaran | >=2500 | NR | 3 to 8 | 100 | 57 | NR | NR | 5 drops/kg | 36 |
| Azadbakht et al. 2005 [27] | Clinical trial | Treatment | NR | Mazandaran | >=2500 | NR | 3 to 8 | 96 | 29 | NR | NR | 5 drops/kg | 48 |
| Azadbakht et al. 2005 [27] | Clinical trial | Treatment | NR | Mazandaran | >=2500 | NR | 3 to 8 | 79 | 12 | NR | NR | 5 drops/kg | 60 |
| Azadbakht et al. 2005 [27] | Clinical trial | Treatment | NR | Mazandaran | >=2500 | NR | 3 to 8 | 65 | 4 | NR | NR | 5 drops/kg | 72 |
| Azadbakht et al. 2005 [27] | Clinical trial | Treatment | NR | Mazandaran | >=2500 | NR | 3 to 8 | 54 | 3 | NR | NR | 5 drops/kg | 84 |
| Azadbakht et al. 2005 [27] | Clinical trial | Treatment | NR | Mazandaran | >=2500 | NR | 3 to 8 | 31 | 2 | NR | NR | 5 drops/kg | 96 |

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NR: Not reported.

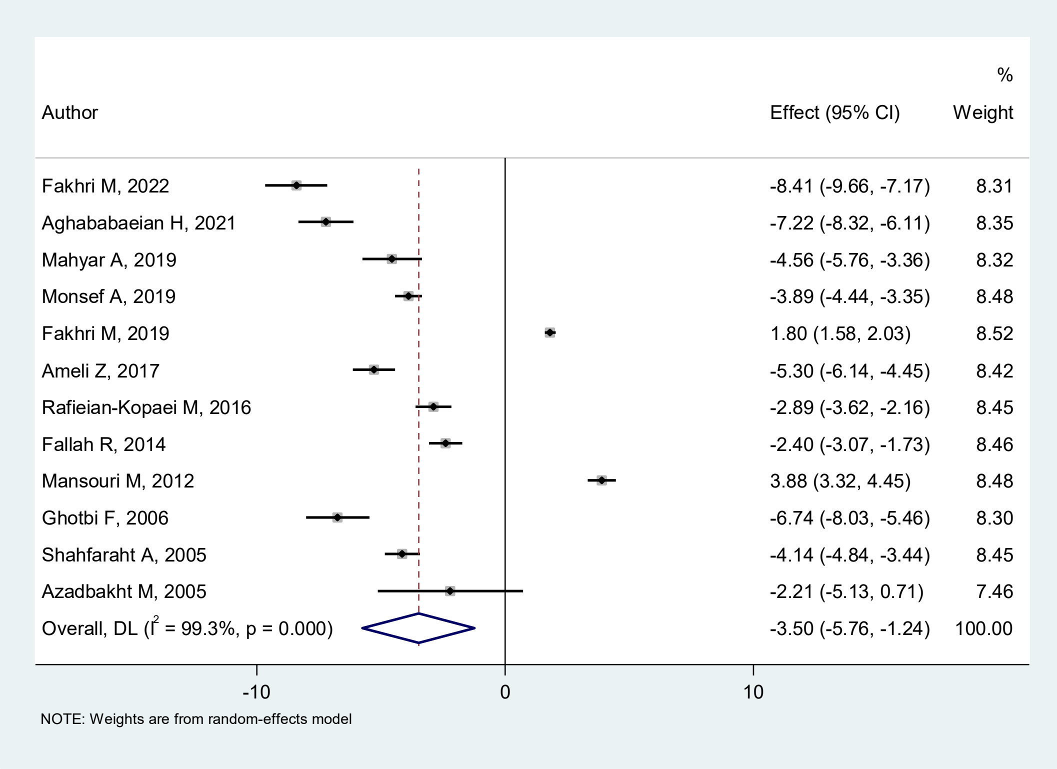


**Figure 2.** Within-group mean difference of bilirubin of newborns in the intervention group

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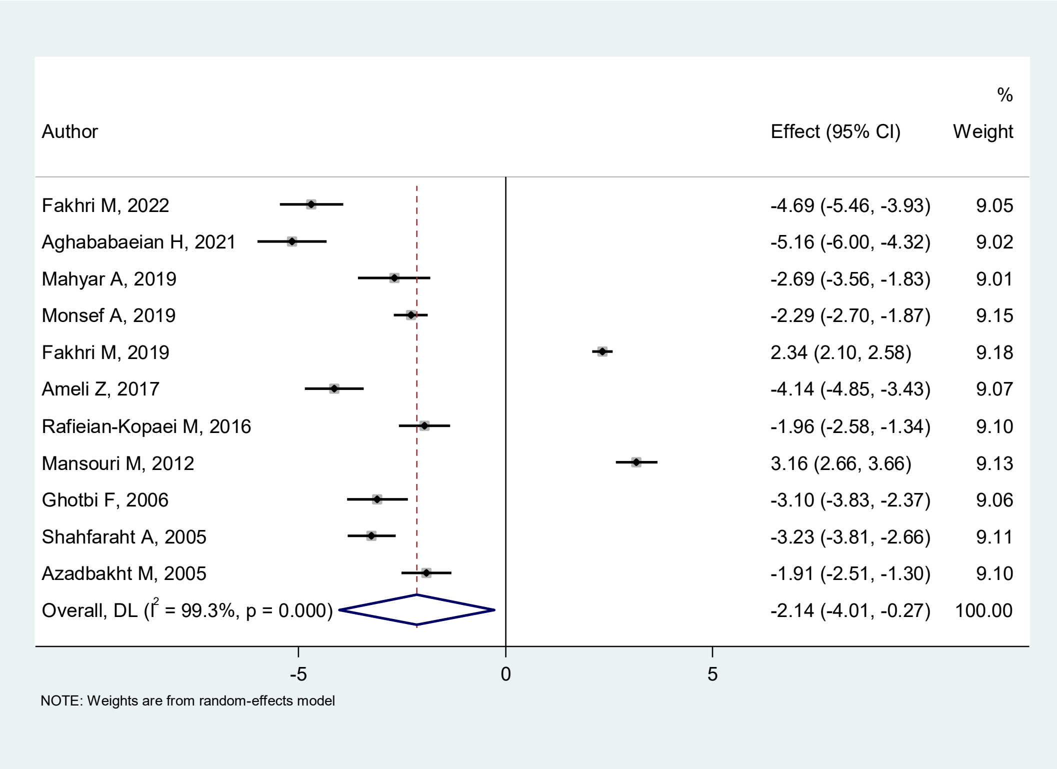


**Figure 3.** Within group mean difference of bilirubin of newborns in the control group

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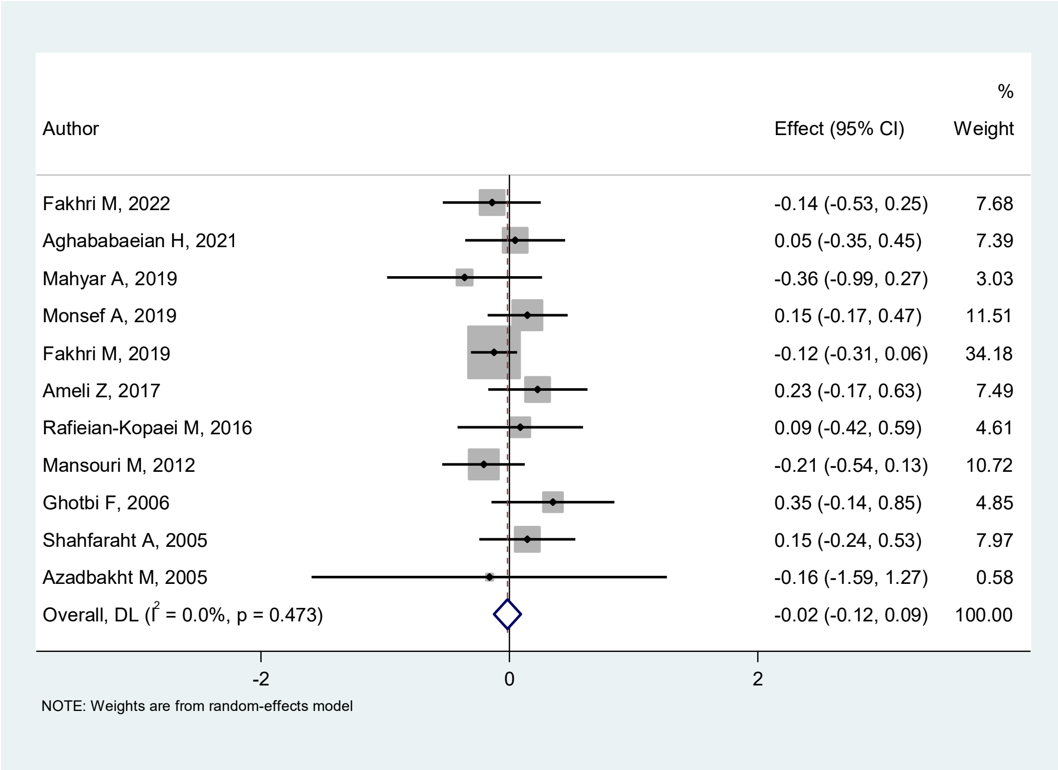


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**Figure 4.** Between groups mean difference of bilirubin of newborns in the intervention and control groups in the pre-intervention phase

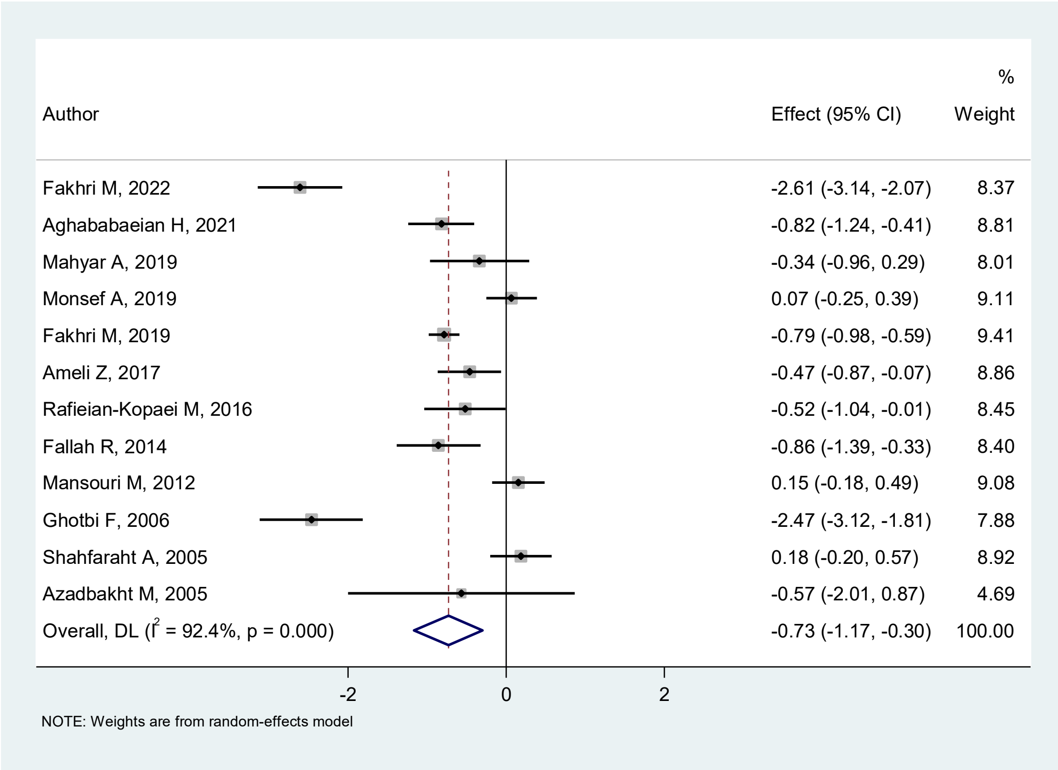


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**Figure 5.** Between groups mean difference of bilirubin of newborns in the intervention and control groups in the post-intervention phase

**Table 2.** Within-group mean difference in serum bilirubin levels of infants at different hours after the intervention in each intervention and control group

| Subgroups | Intervention | | | Compare | | |
|---|---|---|---|---|---|---|
| | SMD (95% CI) | P | $I^2$ (%) | SMD (95% CI) | P | $I^2$ (%) |
| After 12 h | -1.36 (-1.85, -0.88) | <0.001 | 85.0 | -0.79 (-1.23, -0.34) | <0.001 | 85.7 |
| After 24 h | -1.94 (-3.11, -0.76) | <0.001 | 98.7 | -1.18 (-2.21, -0.15) | <0.001 | 98.5 |
| After 36 h | -3.58 (-4.79, -2.37) | <0.001 | 94 | -2.27 (-3.35, -1.19) | <0.001 | 95.6 |
| After 48 h | -3.05 (-5.02, -1.09) | <0.001 | 99.2 | -2.03 (-3.66, -0.41) | <0.001 | 99.2 |
| After 60 h | -3.10 (-5.20, -1) | 0.001 | 91.6 | -2.28 (-4.12, -0.45) | <0.001 | 96.6 |
| After 72 h | -2.19 (-4.96, 0.58) | <0.001 | 99.4 | -1.40 (-3.58, 0.79) | <0.001 | 99.4 |
| After 84 h | -1.63 (-3.58, 0.33) | - | 0 | -1.87 (-2.32, -1.42) | - | 0 |
| After 96 h | -3.69 (-4.76, -2.62) | 0.268 | 18.6 | -2.16 (-2.51, -1.81) | 0.306 | 4.4 |

SMD: Standardized error of the mean; CI: Confidence interval.

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Conversely, in the control group, at time intervals of 12 h, 24 h, 36 hours, 48 h, 60 h, 84 hours, and 96 h after phototherapy, the bilirubin levels of infants significantly decreased. However, no statistically significant effect on the bilirubin levels of infants was observed at 72 h after phototherapy. As seen in both the intervention and control groups, bilirubin levels in infants did not decrease 72 h after the intervention (Table 2).

In Table 3, by comparing the scores between the two intervention and control groups, in time intervals of 12 h, 24 h, 36 h, 48 h, and 72 h after the intervention, the serum bilirubin levels of the *Cotoneaster* group were lower than those of the control group. However, at time intervals of 60 h, 84 h, and 96 h after the intervention, no statistically significant difference in bilirubin levels in infants between the two groups was observed. Overall, in all the studied time intervals, either the effect of *Cotoneaster* was better than phototherapy or it was equivalent to phototherapy (Table 3).

## Additional analyses

Meta-regression in Figure 6 showed no statistically significant correlation between the effect of *Cotoneaster* on reducing the bilirubin levels of infants and the publication year of the studies (P=0.582). In other words, the effectiveness of *Cotoneaster* in reducing the bilirubin levels of infants did not decrease over time from 2005 to 2022.

**Table 3.** Between-group mean difference in serum bilirubin levels of infants after treatment (comparison of intervention and control groups with each other) in different hours after the intervention

| Subgroups | SMD (95% CI) | P | $I^2$ (%) |
|---|---|---|---|
| After 12 h | -0.45 (-0.80, -0.10) | <0.001 | 78.1 |
| After 24 h | -0.63 (-1, -0.26) | <0.001 | 90.4 |
| After 36 h | -0.95 (-1.69, -0.20) | <0.001 | 93 |
| After 48 h | -0.62 (-0.92, -0.31) | <0.001 | 83.6 |
| After 60 h | -0.24 (-1.12, 0.65) | 0.014 | 83.3 |
| After 72 h | -0.84 (-1.40, -0.29) | <0.001 | 93.1 |
| After 84 h | -0.27 (-1.43, 0.90) | - | 0 |
| After 96 h | 0.04 (-0.28, 0.35) | 0.397 | 0 |

SMD: Standardized error of the mean; CI: Confidence interval.

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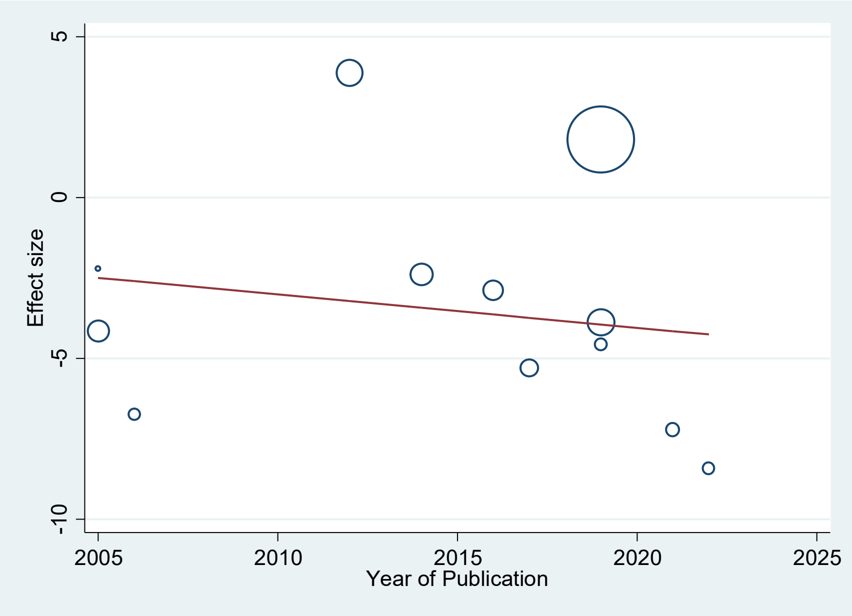


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**Figure 6.** Meta-regression of the relationship between the standard effect size of the effects of *Cotoneaster* consumption on the reduction of bilirubin level in newborns with the year of publication of the articles

Meta-regression indicated no statistically significant relationship between the effect of *Cotoneaster* on reducing the bilirubin levels of infants and the sample size of the studies (P=0.104). Accordingly, *Cotoneaster's* effect on reducing the bilirubin levels of infants was not reported more in studies with larger sample sizes and vice versa (Figure 7).

The funnel plot for publication bias was statistically significant (P=0.004) and indicated that studies reporting the effectiveness of *Cotoneaster* in reducing the bilirubin levels of infants had a higher chance of being published (Figure 8).

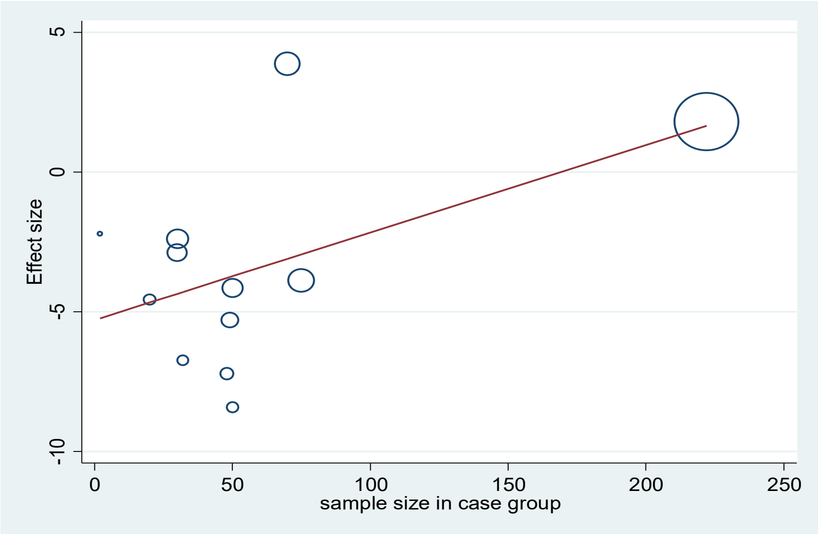


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**Figure 7.** Meta-regression of the relationship between the standard effect size of the effect of *Cotoneaster* consumption on the reduction of bilirubin level in newborns with the sample size of the articles

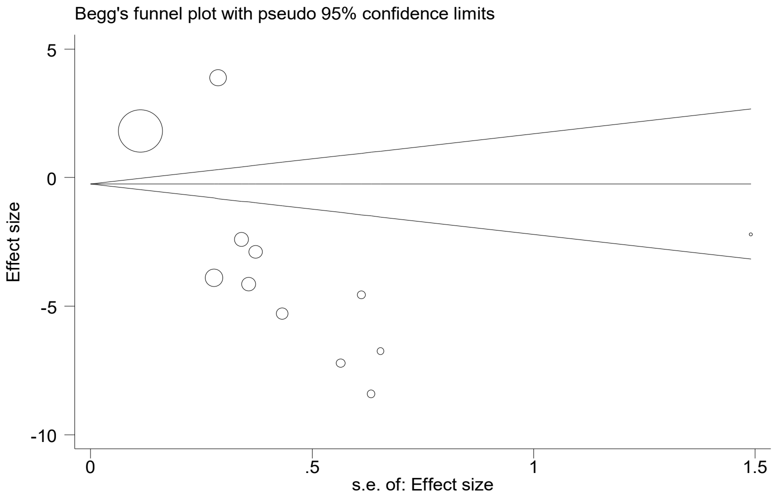


**Figure 8.** Publication bias plot

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## Discussion

Based on the results of our study, overall, the use of *Cotoneaster* is more effective than phototherapy alone in reducing the serum bilirubin levels of infants, and jaundice in the *Cotoneaster* group significantly improved compared to the control group.

In a systematic review by Khedmat et al. (2021), *Cotoneaster manna* was identified as the most important herbal remedy for the treatment of neonatal hyperbilirubinemia. The administration of *Cotoneaster* drops, pomegranate paste and chicory extract by mothers led to a reduction in serum bilirubin and the duration of hospitalization [28]. In a meta-analysis conducted by Fakhri et al. (2018), involving eight clinical trials with a total of 862 infants and aiming to evaluate the effects of *C. manna* on neonatal jaundice, *C. manna* was more effective than phototherapy in the treatment of neonatal jaundice [29]. Sajedi et al. (2019), in a meta-analysis comprising seven controlled randomized clinical trials with 812 infants and investigated the effect of *P. manna* on non-conjugated hyperbilirubinemia in neonates, showed that the levels of bilirubin at 12 h (weighted mean difference [WMD]=-1.48; 95% CI, -2.31%, -0.65%), 24 h (WMD=-2.47; 95% CI, -3.22%, -1.71%), 36 h (WMD:-2.83; 95% CI, -4.87%, -0.80%), 48 h (WMD=-1.49; 95% CI, -2.36%, -0.63%) and 72 h (WMD=-0.68; 95% CI, -1.28%, -0.08%) after the intervention were significantly lower in the *P. manna* group [12]. In a meta-analysis conducted by Salehi et al. (2018), involving seven studies with 804 participants, the overall plasma bilirubin levels at 0, 12, 24, 36, and 48 h were examined. Furthermore, the effects of *Cotoneaster* on reducing neonatal jaundice were demonstrated (odd ratio (OR)=0.242; 95% CI, 0.147%, 0.399%; P<0.0001) [30]. The results of the current meta-analysis were consistent with the findings of these studies. The advantage of our study over previous meta-analyses was that it was more up-to-date and included a larger number of studies (12 clinical trials) for investigation. The number of neonatal samples in our meta-analysis (1557 neonates) was nearly twice the number of neonatal samples in previous meta-analyses. The results obtained from a larger population have greater reliability.

In a study by Shah Farhat in 2002, the serum bilirubin level after treatment with *Cotoneaster* did not show a statistically significant difference between the intervention and control groups. This study demonstrated that the consumption of 6 grams of *Cotoneaster* for the treatment of neonatal jaundice is not more effective than a placebo [14]. Nabavizadeh et al. conducted an in vitro study in which they aimed to investigate the effects of herbal medicines on neonatal hyperbilirubinemia. They reported that although jujube, *Cotoneaster*, and manna of Hedysarum are mild laxatives and can reduce the enterohepatic circulation of bilirubin in the intestine and promote intestinal bilirubin excretion, only chicory can effectively reduce bilirubin levels outside the body and without the influence of internal factors [31]. The results of the study by Rahani showed no statistically significant difference in the rate of bilirubin reduction in serum between the field massage group and the group receiving synthetic oral *Cotoneaster* drops (bilineaster) and the control group. Despite traditional beliefs in the efficacy of *Cotoneaster*, it did not affect reducing jaundice in neonates undergoing phototherapy [32]. These studies indicated that the consumption of *Cotoneaster* does not have a statistically significant effect on neonatal bilirubin levels and is not effective in reducing neonatal jaundice. Therefore, the results of these studies were not in line with the findings of the current meta-analysis. However, factors, such as differences in the type of study, sample size, and variations in the weight, age, and gender of the infants under investigation may have contributed to these differences in results. Of course, other issues are involved in the jaundice of babies, a randomized clinical trial study was conducted on 88 infants with jaundice. Both groups received standard conventional phototherapy and the intervention group received 5 drops of probiotic until hospital discharge and the comparison group received a placebo then the results showed that the probiotic group had a significantly lower hospitalization stay in comparison to the placebo group [33]. And in another study, there was a significant relationship between maternal normal serum vitamin D levels with neonatal 14th day jaundice [34].

## Conclusion

Following the intervention, the bilirubin levels of neonates who received *Cotoneaster* were generally lower than those in the control group, which only received phototherapy. As the control group received phototherapy, it was natural that their bilirubin levels also decreased, and in some phases of the study, no significant difference was observed between the two groups. However, in most stages of the study, the condition of jaundiced neonates in the *Cotoneaster* group was better than that of the control group. In the future, healthcare professionals may consider using *Cotoneaster* alongside phototherapy to reduce neonatal bilirubin levels further, potentially reducing the duration of phototherapy and hospitalization and associated costs.

### Study limitations

Since the studies included in our analysis did not report the effect of *Cotoneaster* on neonatal bilirubin levels based on variables, such as the gender of the neonates or the type of maternal delivery (cesarean section vs vaginal delivery), we were unable to compare the effect of *Cotoneaster* on bilirubin levels between male and female neonates or between neonates born through cesarean section and those born through vaginal delivery. Meanwhile, in the studies examined, the age and weight ranges of the neonates were such that they could not be categorized effectively. Therefore, in subgroup analyses, we were unable to assess the effect of *Cotoneaster* on neonatal bilirubin levels based on variables such as the age and weight of the neonates. Similarly, it was not possible to evaluate the effect of *Cotoneaster* on neonatal bilirubin levels based on the dosage of *Cotoneaster* consumed. It is recommended that these limitations be addressed in future studies.

## Ethical Considerations

### Compliance with ethical guidelines

This protocol was registered by the PROSPERO registry (Code: CRD42023457218).


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### Authors contributions

Conceptualization, study design, data analysis and results interpretation: Moloud Fakhri; Review, editing and final approval: All authors.

### Conflicts of interest

The authors declared no conflict of interest.


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