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A systematic review and Meta-Analysis on the effect of *Cotoneaster manna* on neonatal jaundice

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ABSTRACT

Background & Aim: The manna of *Cotoneaster nummularia* (purgative manna) has been traditionally used in the Persian medicine for the treatment of neonatal jaundice. The effect of *Cotoneaster manna* on neonatal jaundice was investigated with systematic review and meta-analysis.

Experimental: This study intended to explore the clinical trials of the efficacy of *Cotoneaster manna* on neonatal jaundice. The aspects considered in this study included searching for relevant English and Persian data bases up to March 2016. The methodological quality was assessed using the Consort checklist for herbal interventions. Seven studies with low or moderate risk of bias involved 804 participants of which 410 cases versus 394 controls were selected for systematic review and meta-analysis with CMA software version 2.2.

Results: Total plasma bilirubin in 0, 12, 24, 36, 48 hours and the duration of hospital stay were checked and no adverse effect was reported. The Meta-analysis exhibited marked heterogeneity of the results (Q-value = 132.446, P< 0.0001, I2 = 87.165, τ = 0.998). However, it showed favorable effect of *Cotoneaster manna* on reducing neonatal jaundice (n= 804, OR = 0.242, 95% CI: 0.147 to 0.399, P< 0.0001). Also it was effective on reducing duration of hospital stay (n= 804, SMD= -1.154, 95% CI: -1.854 to -0.455, P< 0.001). However, the results obtained were heterogeneous (Q-value= 119.642, P< 0.0001, I2= 94.985, τ= 0.913).

Recommended applications/ industries: Although the meta-analysis of *Cotoneaster manna* showed positive effect on treatment of neonatal jaundice in these studies, it is warranted to carry out further multi-centre randomized clinical trials with larger samples and controlled risk factors, alongside comparison with phototherapy.

1.Introduction

Neonatal jaundice is one of the most common problems of infancy characterized by increasing serum bilirubin. The main cause of this disease is glucuronyl transferase deficiency, which affects about 60% of term and 80% of preterm infants (Kliegman and Stanton, 2016;

Newman and Maisels, 1992). Physiologic jaundice is the most common cause of neonatal jaundice in which indirect serum bilirubin increases are found up to 12mg/dl in 3rdand up to 15mg/dl in 5thpost-natal days (Gürhan *et al.*, 2007; Kliegman *et al.*, 2016). Other causes of the disease arebreast feeding, breast milk and Crigler- Najjar (Newman and Maisels, 1992). One of the most serious side effect of neonatal jaundice is kernicterus or bilirubin encephalopathy that can lead to severe brain damage, sensorineural hearing loss, seizure and ultimately death (Hansen, 2000; Khalid *etal*., 2015). The current therapy for neonatal jaundice is phototherapy and as the last choice is blood exchange to rapidly decrease serum bilirubin concentration (Ennever, 1990; Tan, 1991). Although these therapies have favorable outcome, they are accompanied by significant side effects (Tan, 1996). The most common side effects of phototherapy include dehydration, fever, diarrhea, rash, irritability, weakness and bronze baby syndrome(Cuvellier *et al*., 1990; Drew *et al*., 1976; Siegfried *et al*., 1992). Also numerous complications including those associated with transfusion and catheter usage may occur during different parts of blood exchange procedure (Fakhri, 2016).

In Traditional Persian Medicine, *Cotoneaster manna* (*C. manna*) is used for treatment of neonatal jaundice (Khodashenas, 2015; Amiri, 2014). Shirekhesht (*Cotoneaster manna*) is the extract of a plant with the scientific name of *Cotoneaster* nummularioides Pojark Fisch. & C. A. Mey. from *Cotoneaster* species and the Rosaceae (Amin, 2013). It is a herbal ingredient that is frequently used in Traditional Persian Medicine(Aghili, 2009). Its physical characteristics are round or amorphous particles either white or yellowish white in texture with sweet and refreshing taste (Amin, 2013). Ancient Iranian scholars have emphasized on its efficacy in liver- related diseases and jaundice by its laxative effect, and was also described in their writings as beneficial in children and the elderly(Aghili, 2009). *Cotoneaster manna* has recently been approved as laxative and the manitol, as its most important ingredient, is found to be responsible for its laxative effectand diarrhea through its osmotic activity (Aynehchi, 1986; Etebari *et al.*, 2012; Warren and Blantz, 1981). Nowadays, clinicians and researchers have become interested in traditional medicine to find alternative therapies for various diseases (Atarzadeh *et al.*, 2016; Heydari, Homayouni *et al.*, 2015; Jafarpour *et al.*, 2016; Mosavat *et al.*, 2015). In recent years many studies have been conducted to treat neonatal jaundice with herbal components of which *Cotoneaster manna* is one of the most common medication (Fallah *et al.*, 2012). Some studies have reported highly favorable results from usingC. manna in the treatment of neonatal jaundice compared to the control group. However, its effect was reported to be insignificant by some other investigations (Amoli, 2010; Farhat *et al.*, 2006; Ghotbi *et al.*, 2006; Shakiba and Pishva, 1992). Due to these discrepancies and lack of a systematic review on this issue, the present study attempted to carry out a systematic review and meta-analysis to provide a definitive and clear-cut conclusion about the efficacious treatment of neonatal jaundice by *C. manna.* The aim of present study was to determine, through systematic review and meta-analysis, the efficacy of *C. manna* in decreasing the level of serum bilirubin and reducing the duration of hospital stay in jaundiced neonates.

2. Materials and Methods

2.1. Protocol

Guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2009 which is available online on http://prisma-statement.org/ were followedto conduct this study (Liberati *et al*., 2009).

2.2. Inclusion Criteria

Inclusion criteria for this study were clinical trials which investigated the effect of *C. manna* on neonatal jaundice. Time limitation was the only reason for not including other studies up to March 2016. In addition, the search was restricted to Persian and English articles. All relevant titles and abstracts, considering inclusion criteria, were read and evaluated by the authors. Some studies were excluded because of being non- clinical, in vitro or investigating the preventive effect of *C.manna*. Also related theses were searched and those without available full text were excluded, despite contact with their author (Amoli, 2010).

2.3. Data Sources

The English data bases searched for this study included Medline, Scopus, Web of Science, Science Direct, Proquest, the Cochrane Central Register of

Controlled Trials (CENTRAL), EMBASE and CINAHL. Other items incorporated in the study were hand searching of neonatology and relevant meeting abstracts. The keywords used comprised "*Cotoneaster nummularia*" OR "*Cotoneaster discolor*" OR "purgative manna" OR Shirkhesht" OR "*Cotoneaster manna*" OR "*Cotoneaster* persicus" OR "billinaster". As for Google Scholar search, "AND (neonatal jaundice OR neonatal hyperbilirubinemia)" was added to the reforegoing keywords, because of numerous articles on the subject. In regard to Persian databases search, using Persian word Shirkhesht, preceded by "the"was done in Iranmedex, SID, Magiran, Irandoc. Available Iranian theses in Irandoc (Iranian research institute for information science and technology) database were also searched for Shirkhesht, where two dissertations were found of which one was excluded because of its unavailable full text.

2.4. Study Selection

Search was done separately by two investigators. Amongst 668 results obtained from the database, 16 were omitted due to duplication. We chose only the name of the drug. The name used in all databases was *C. manna*, except Google Scholar, because most of the articles were not related to neonatal jaundice. The titles and abstracts of all articles were checked, of which 22 were related to neonatal jaundice and 630 were excluded.

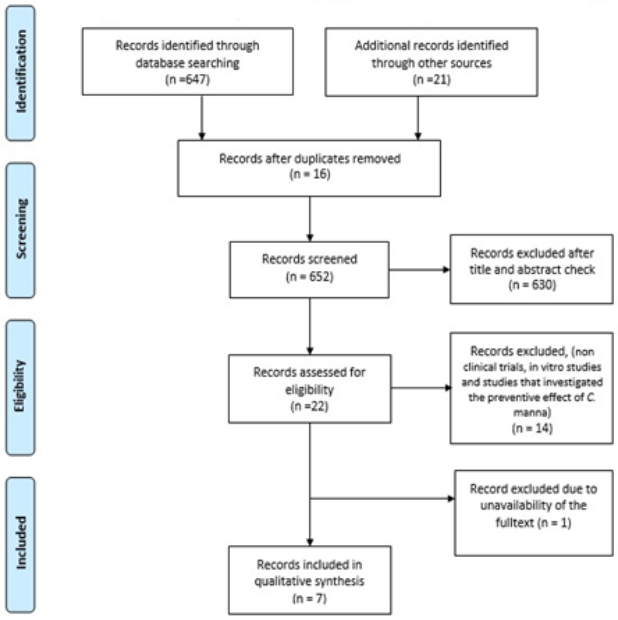


Figure 1. The Flow diagram of the study according to PRISMA 2009 flow chart.

The studies were then reviewed for their relevance, and eight clinical trials on the effect of *C. manna* on neonatal jaundice were selected. Also, one study was excluded because of unavailable full text (Amoli, 2010). Finally, seven studies were included in this systematic review and meta-analysis of which four were in English and two in Persian and one Persian thesis (Azadbakht *et al.*, 2005; Fallah *et al.*, 2014; Farhat *et al.*, 2006; Ghotbi *et al.*, 2006; Rafieian-Kopaei *et al.*, 2016; Reshadmanesh *et al.*, 2001; Shakiba and Pishva, 1992). Figure 1 shows flow diagram of the study according to PRISMA 2009 flow diagram (Figure1).

2.5. Quality and validity assessment

The methodological quality of the included trials, in terms of internal validity, was assessed by the reviewer's MO and AS using the Jadad scale. Then, if the assessments of two authors were incompatible, the differences were resolved by discussion, and obtaining the opinion of the third reviewer (MM). Various biases with respect to selection, performance, detection and attrition were evaluated in terms of randomization, blinding of intervention and account of all patients. Studies gaining total score of three or more were selected (Table 1).

2.6. Data Extraction

Data were extracted from each study separately by MO and AS,using custom made data collection form, considering a number of criteria. These included first author, publication year, journal ISSN, dose, frequency and duration of intervention, serum bilirubin level at 0, 12, 24, 36, 48 hours after admission, days of hospital stay, number of subjects, number of groups, comparison group (s), characteristics of neonates, and finally key results, of which some are shown in Table2. Only published data were analyzed, thus it was not necessary to contact the authors for verification. Serum bilirubin levels were checked inall studies,except in two cases where this was not reported(Reshadmanesh et al., 2001; Shakiba and Pishva, 1992), and the number of hospitalization days were recorded in all studies. In these studies, the populationswere newborns admitted to hospitals with diagnosis of neonatal jaundice. All participants, in both the intervention and control groups, received phototherapy under the same condition. In most of the studies, blindness was applied and control group received placebo (Azadbakht *et al.*,

2005; Farhat *et al*., 2006; Ghotbi *et al.*, 2006; Rafieian-Kopaei *et al.*, 2016; Reshadmanesh *et al.*, 2001). Due to the patients are neonates it was not necessary to blind them. Also blindness is impossible for therapists to the use of drug in two of the studies due to the type of the drug which is used in the third group of patients(Fallah *et al.*, 2014; Shakiba and Pishva, 1992).The treatment of jaundiced neonates with *C. manna* was safe and without any significant adverse effect.

Table 1. Jadad scale for quality and validity assessment of the selected studies which evaluate the effectiveness of *C. manna* on neonatal jaundice.

Author	Randomization 1	Method of randomization 1	Blindin 1	Method of blinding 1	An account of all patients 1	Total 5
M. Rafieian*et al.*, 2016	1	1	1	1	0	4
R. Fallah *et al.*, 2014	1	1	1	1	1	5
F. Ghotbi *et al.*, 2006	1	0	1	1	1	4
A. Shah Farhat *et al*., 2006	0	0	1	1	1	3
M. Azadbakht *et al.*, 2005	1	1	1	1	1	5
N. Reshadmanesh *et al.*, 1998	1	1	1	1	1	5
M. Shakiba *et al.*, 1992	1	1	0	0	1	3

Table2. Characteristics of the selected studies which evaluate the effectiveness of *C. manna* on neonatal jaundice.

Author	Duration of Int.	Dose of Int.	NO of subjects	Other group(s) NO.	Comparison group(s)	Key results	characteristics of neonates
M. Rafieian *et al.*, 2016	24h	3 drop/kg Q8h (B®)	60	3	Placebo, *C. manna* to mother, *C. manna* to both mother and neonates	P<0.05	Bili=14-20, MABL:16.33, Bwt=2500-4000, GA=37-42, BF, age> 2d/o
R. Fallah *et al*., 2014	48h	5 drop/kg Q8h (B®)	60	2	Control, Glycerin suppository	P=0.02*	Bili=15-20, MABL:17.6, Bwt=2500-4000, GA=37-42, BF Age>2 d/o, NVD,
F. Ghotbi *et al.*,[1] 2006	24h	10cc TID of 16% solution	64	1	placebo	P<0.001	Bili=15-20, MABL: 17.1, Bwt=2500-4000, GA=37-42, BF, Age: 3-11 d/o
A. Shah Farhat *et al*., 2006	Single dose	6 grams	104	1	placebo	Not Sig	Bili=18-29, MABL:23.4, Bwt>2500, BF, adjusted weight
M. Azadbakht *et al., 2005*	24h	5 drop Q8h (610 mg/cc)	200	1	placebo	P=0.00001	MABL:17.1, term, adjusted sex
N. Reshadmanesh *et al.*,[2] 1998	Till discharge	20 cc Q8h (1 g in 30 cc water)	136	1	placebo	P<0.00	Bili>10 adjusted with weight and age, feeding, and delivery
M. Shakiba *et al.*,[3] 1992	Single dose	400 mg	180	2	Nothing , Camel's thorn manna	P=0.00001	Bili<20, MABL:16.3, Bwt>2500, term,

Int.: intervention, NO.: number, , Bili: Bilirubin, MABL: mean admission serum bilirubin level, Bwt: Birth weight, GA: Gestational Age, BF: breastfed d/o: days old, B®: bilinaster drop, Sig: Significant, NVD: Natural Vaginal Delivery, Q8h: every 8 hours, TID: three times a day, [1, 2, 3]: Persian studies

* P-value of decreasing serum bilirubin level by *C. manna* compare to control group in all studies except in fallah et al. that P- value after 24 and 48 hours of admission is mentioned.

2.7. Data synthesis

The effect of *C.manna* on reducing neonatal jaundice was expressed as mean change of serum bilirubin levels and duration of hospital stay in all the studies. A change in mean serum bilirubin levels to Odds Ratio (0R) was observed by using meta-analysis software (CMA) version 2.2.064 and incorporating the existing formulas. Therefore, OR and 95% confidence intervals (CIs) were determined from each study for meta-analysis of serum bilirubin levels which showed the efficacy of intervention compared to the control. The serum bilirubin levels were evaluated in 5 categories at 0, 12, 24, 36, 48 hours after admission. The Q test, τ andI^2 were used to assess heterogeneity.

3. Results and discussion

The primary outcome was decreasing serum bilirubin level at 0, 12, 24, 36, 48 hours after admission expressed as Mean ± SD in the control and intervention group. However, in two studies, serum bilirubin levels were not reported (Reshadmanesh *et al*., 2001; Shakiba and Pishva, 1992), but indicated a reduction in the intervention group compared to the control group. All the studies, except that of Shah Farhat *et al.*(Rafieian-Kopaei *et al*., 2016) reported significant effect of *C.* manna on neonatal jaundice (P value< 0.05).

Mean admission serum bilirubin level was less than 20 mg/dl in all the studies, except in 2 reports(Farhat *et al.*, 2006; Reshadmanesh *et al*., 2001).This was not indicated in Reshadmanesh *et al*. (2001)study which involved multiple subgroups, where the mean serum bilirubin level was reported separately for each subgroup, but not as a whole (Reshadmanesh *et al.*, 2001). On the other hand, Shah Farhat *et al.*(2006) reported the bilirubin levelas23.4, since 18-29 was one of the inclusion criteria (Farhat *et al*., 2006). Therefore, serum bilirubin level in this study was higher compared to those of other investigations (Azadbakht *et al.*, 2005; Fallah *et al*., 2014; Ghotbi *et al.*, 2006; Rafieian-Kopaei *et al*., 2016; Shakiba and Pishva, 1992).

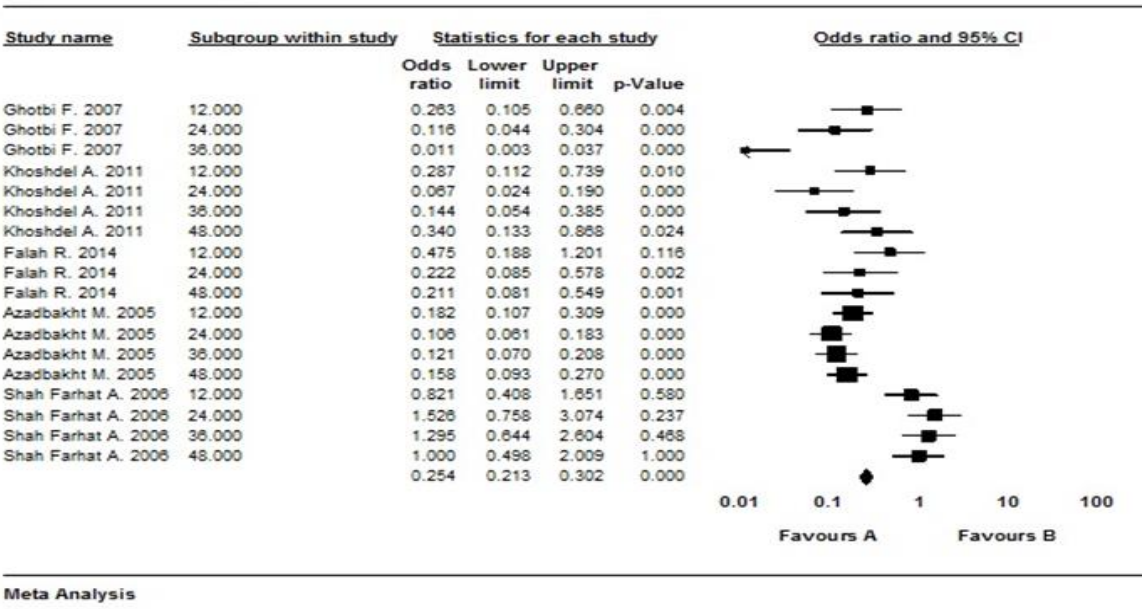
Variations were found in some of the characteristics of these studies (Table 2).

These included the duration of intervention from single dose until discharge (Farhat *et al.*, 2006; Shakiba and Pishva, 1992; Reshadmanesh *et al*., 2001). Also the total number of participants in these seven studies was 804 that varied from 60 to 200 in eachstudy (Azadbakht *et al.*, 2005; Fallah *et al.*, 2014; Rafieian-Kopaei *et al.*, 2016). In all investigations, *C. manna* was given three times per day, except in two studies where it was given as a single dose (Farhat *et al.*, 2006; Shakiba and Pishva, 1992). Five studies included term (GA=37-42) only infants (Azadbakht *et al.*, 2005; Fallah *et al*., 2014; Ghotbi *et al*., 2006; Rafieian-Kopaei *et al.*, 2016; Shakiba and Pishva, 1992), but in two studies this was not mentioned as an inclusion criteria(Farhat *et al.*, 2006; Reshadmanesh *et al*., 2001). In four studies, neonates were breastfed (Fallah *et al*., 2014; Farhat *et al.*, 2006; Ghotbi *et al*., 2006; Rafieian-Kopaei *et al.*, 2016),but other studies comprised both formula-fed and breastfed neonates (Azadbakht *et al.*, 2005; Reshadmanesh *et al.*, 2001; Shakiba and Pishva, 1992). Neonates in five studies had birth weight more than 2500 gram (Fallah *et al*., 2014; Farhat *et al*., 2006; Ghotbi *et al.*, 2006; Rafieian-Kopaei *et al*., 2016; Shakiba and Pishva, 1992) an evidence of significant variations in characteristics.

In all these studies the focus was on two outcomesserum bilirubin level and duration of hospital stay**,**butdue to the laxative effect of *C. manna*, the frequency of passing stool per day was taken into account in three (Fallah *et al.*, 2014; Farhat *et al.*, 2006; Ghotbi *et al.*, 2006),whereas two studies indicated an increase in bowel movement (Fallah *et al.*, 2014; Ghotbi *et al.*, 2006). As shown in Figure 2, the Meta-analysis by using random effect exhibited marked heterogeneity of the results (Q-value = 132.446, P< 0.0001, I^2 = 87.165, τ = 0.998), but it showed favorable effect of *C. manna* on reducing bilirubin levels(n= 804, OR = 0.242, 95% CI: 0.147 to 0.399, P< 0.0001), where its effect was most significant after 36 hours of admission.

The statistical analysis of the meta-analysis results related to 12, 24, 36 and 48 hours after admission were (OR = 0.351, 95% CI: 0.123 to 1.002, P=0.05), (OR= 0.199, 95% CI: 0.069 to 0.573, P=0.003), (OR= 0.138, 95% CI: 0.042 to 0.451, P=0.001) and (OR= 0.326, 95% CI: 0.101 to 1.053, P=0.061), respectively. As for the duration of hospital stay, the meta-analysis showedsignificant heterogeneity of the results (Q-value= 119.642, P< 0.0001, I^2= 94.985, τ= 0.913). Using random effect, a reduction in duration of hospital stay (n= 804, SMD= -1.154, 95% CI: -1.854 to -0.455, P< 0.001) was observed following treatment of jaundiced neonates with *C. manna* (Figure 3).

Figure 2. Meta-analysis of mean serum bilirubin levels reported in the selected studies which evaluate the effectiveness.



This study is the first systematic review and meta-analysis on the therapeutic effect of *C. manna* on neonatal jaundice. Our result indicates that *C. manna* is efficient in decreasing serum bilirubin level as well as reducing hospital stay in neonates admitted for neonatal jaundice.

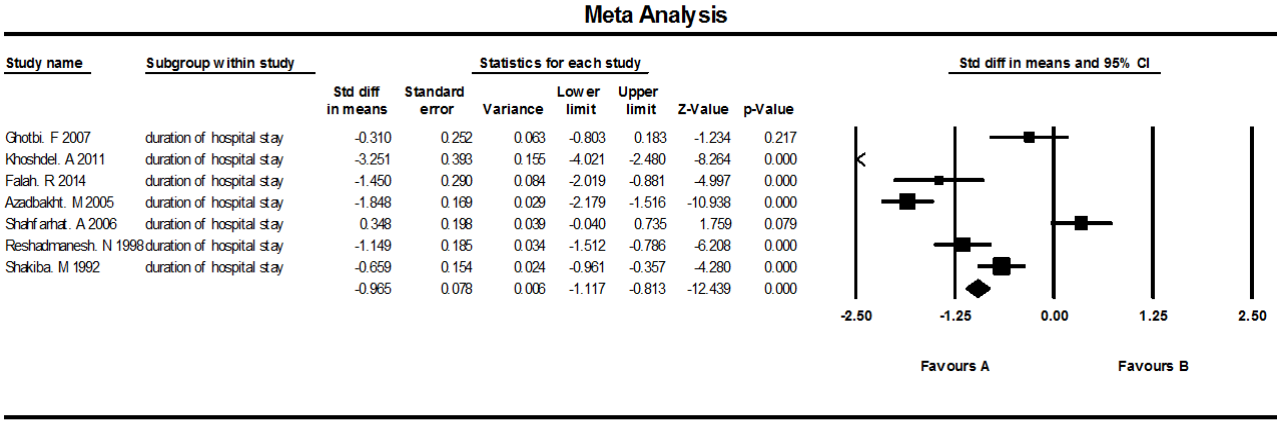
The reduction in hospital stay of the jaundiced neonates by oraladministration of *C. manna* is of great value both for the patients and health system. Neonatal jaundice and its complications have a high global burden and its emergency treatment is a part of cost-effective measures for reducing neonatal mortality(Adam *et al.*, 2005; Olusanya, Akande, Emokpae, and Olowe, 2009). Therefore, the role of *C. manna* in decreasing the duration of hospital stay of jaundiced neonates is an efficient approach in reducing this high burden and neonatal mortality.

All selected studies indicate the efficiency of *C. manna* in reducing serum bilirubin level, exceptShah Farhat *et al*. (2006)study which reported*C. manna* to be ineffective in treating neonatal jaundic may be due tothe higher level of bilirubin in their patients(Shakiba and Pishva, 1992). This hypothesis is confirmed by the highfrequency of daily passage of stooldue to laxative effect of *C. manna*, but they reported no difference between intervention and control group.

Despite pathological causes due todisease, drug and maternal diseases, there are severalimportantfactors such as gestational age at birth, breast feeding, and method of delivery, sex, race and weight which may be involved indevelopment of neonatal jaundice.These should be considered in future studies of neonatal jaundice especially in those with younger gestational age (less than 38 weeks) (Maisels, 2006; Newman *et al.*, 1999). Exclusive breastfeeding is a strong risk factor for the development of hyperbilirubinemia (Bertini *et al.*, 2001; Maisels and Gifford, 1986; Muchowski, 2014). Bilirubin levels of the infants born through vaginal delivery without complication are significantly higher than thosedelivered by caesarean section (Maisels and Gifford, 1986; Yamauchi and Yamauchi, 1989). *Male* neonates are more prone to sever hyperbilirubinemia than females(Najib *et al.*, 2013; Newman *et al.*, 1999). East Asian race is a major risk factor for development of neonatal jaundice (Bertini *et al.*, 2001; Kliegman and Stanton, 2016; Newman *et al.*, 1999). The Infants with lower birth weight have a higher mean bilirubin concentration than heavier new-borns (Friedman *et al.*, 1978). Few studies have reported the risk of hyperbilirubinemia for very low birth weight (VLBW) neonates (Watchko and Maisels, 2003).So, these factors should be controlled in randomized clinical trials to show the actual effect of *C. manna* on neonatal jaundice. Some of the foregoing factors were adjusted or measured in these seven selected studies but significant heterogeneity and

variation was reported in regard to the characteristics of participants and the risk factors involved. The most principal difference, in these studies, was the difference in dosage, frequency and duration of *C. manna* administration.

Figure 3. Meta-analysis of duration of hospital stay reported in the seiected studies which evaiuate the effectiveness of *C. manna* on neonatal jaundice.



As mentioned, meta-analysis showed that the most effective time is 36 hours after admission, but the effective dose and its frequency should be investigated by large sample multi-centre clinical trials to compare different doses and risk factors under similar conditions .Also measuring the factors related to the mechanism of action of *C. manna*, such as the frequency of passing stool per day and the amount of bilirubin in stool, can help to determine the effective dose.

The limitations of this study are the lack of access to the full text of the thesis due to the need of author's permission, and searching of the databases only in relation to English and Persian articles. Therefore, future reviews in other languages should be performed in order to verify our findings.

4. Conclusion

The meta-analysis performed in this study showed a positive effect of *C. manna* on treatment of neonatal jaundice by reducing both the serum bilirubin level and the duration of hospital stay. However, more randomized clinical trials with larger samples and controlled risk factors, compared with phototherapy are needed to fully support the efficient treatment of jaundiced neonates with *C. manna*.

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