Original Article

The effect of Bilineaster "Cotoneaster" on reducing bilirubin in neonates with jaundice -a triple-blind randomized clinical trial

Hamidreza Aghababaeian[1,2], Fereidon Nirouzad[1], Maryam Kiarsi[1], Neda Amirgholami[3], Leila Kalani[1], Reza Beiranvand[2], Ali Sadeghi Moghaddam[1], Omid Zakeri[1], Narges Majidipour[1]*

[1]Dezful University of Medical Sciences, Dezful, Iran. [2]Tehran University of Medical Sciences, Tehran, Iran. [3]Faculty of Pharmacy Ahvaz Jundishapour University of Medical Sciences, Ahvaz, Iran.

Correspondence: Narges Majidi, Dezful University of Medical Sciences, Dezful, Iran. Majidipour.n@dums.ac.ir

ABSTRACT

Jaundice is one of the most common concerns in neonates. In Iran, the extract of *Cotoneaster frigidus* is used to reduce physiologic jaundice according to traditional medicines. This study aimed to investigate the effect of medication "Bilineaster" on the reduction of jaundice in neonates. This study was a randomized, triple-blind clinical trial. In this study, 96 neonates with physiologic jaundice referred to a pediatric clinic in Dezful were selected by the available sampling method. After assessing the required laboratory tests, they were randomly allocated into the case and control groups. In this study, in addition to phototherapy, *Cotoneaster frigidus* extract and placebo were administered to the case and control groups, respectively, and the level of bilirubin was checked every 24 hours for 72 hours after initiation of treatment. The gathered data were analyzed using the chi-square test, independent t-test, and ANOVA by SPSS software. There was no significant difference between the experimental and control groups regarding gender, age, birth weight, hemoglobin level, type of delivery, G6PD enzyme, and total bilirubin level at baseline ($p>0.05$). The analysis of variance with repeated measures showed that there was a significant difference in serum bilirubin levels between the two groups at 48 and 72 hours after initiation of the treatment ($p\leq0.05$). This study indicated that the consumption of Bilineaster drop is effective in the reduction of bilirubin serum levels in neonates.

Keywords: Jaundice, Neonates, Cotoneaster frigidus, Herbal medicine, Iranian medicine

Introduction

Jaundice is one of the most common causes of neonatal diseases and their hospitalization in the first weeks of life around the world [1]. Jaundice occurs in more than 50-60% of term neonates and 80% of preterm infants, and accounts for about 13.5% of all hospital admissions for neonates [2]. Meanwhile, approximately 1.1 million newborns are affected with severe hyperbilirubinemia each year, with the majority being in South Africa and Asia [3]. In general, severe hyperbilirubinemia occurs in at least 481,000 term or preterm infants around the world, out of whom 114,000 die, and more than 63,000 neonates develop moderate or severe disability [4]. Nowadays, in developed countries such as Canada, the highest incidence of hyperbilirubinemia ranges from 1 per 67,000 to 1 per 44,000 live births [3]. Neonatal jaundice or hyperbilirubinemia refers to jaundice at birth or at any time during the infancy. In this disease, bilirubin pigments accumulate in the skin, mucous membranes, sclera, and other organs. The cause of jaundice is an excessive increase in serum indirect bilirubin levels to ≥171 µmol/L for preterm infants and ≥256 µmol/L for term neonates [4]. Jaundice can be physiological or pathological; physiological jaundice develops in the first week after delivery as a result of

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Aghababaeian H, Nirouzad F, Kiarsi M, Amirgholami N, Kalani L, Beiranvand R, et al. The effect of Bilineaster "Cotoneaster" on reducing bilirubin in neonates with jaundice -a triple-blind randomized clinical trial. J Adv Pharm Educ Res. 2021;11(1):23-8. https://doi.org/10.51847/qABgSKl

increases in bilirubin production due to the destruction of fetal erythrocytes with transient restrictions in conjugated bilirubin, which is often mild and sometimes does not require any treatments. On the other hand, pathological jaundice usually occurs within the first 24 hours or after the first week of birth [5]. In pathological jaundice, increased production of non-conjugated bilirubin decreases hepatic uptake, and increased bilirubin enterohepatic cycle leads to increased non-conjugated bilirubin [6]. Non-conjugated bilirubin is a neurotoxin whose high levels can cause kernicterus and cerebral encephalopathy resulting in mental retardation and permanent neurological damage [7]. Clinical interventions for jaundice include phototherapy; administration of chemical medications such as phenobarbital; and complete or partial blood exchange transfusion. Given many complications of exchange transfusion in neonates including hypoglycemia, hypocalcemia, the risk of sepsis, thrombocytopenia, and even death [5], it may be the last choice to reduce bilirubin level in cases of jaundice who do not respond to other treatments [8]. Phototherapy is the most common intervention for the prevention and treatment of severe hyperbilirubinemia [9]. Although phototherapy is a non-invasive and acceptable treatment, it has side effects such as hypovolemia, diarrhea, cutaneous melanocyte and erythematosus rashes, hyperthermia, sideroderma infant syndrome, hypocalcemia, impaired normal body rhythms, and allergic diseases [10]. Moreover, phototherapy has limited efficacy at high levels of serum bilirubin, which is associated with complications such as encephalopathy and kernicterus [7]. Several studies have also examined the adverse effects of phenobarbital on infants. These findings suggest that phenobarbital increases the enzymatic activity of hepatic cells, thereby increasing the metabolism of several medications and reducing their effects. Therefore, an attempt to reduce serum bilirubin levels with no side effects seems necessary [10]. In this regard, some researchers have considered traditional medicine remedies, especially the use of herbs. For example, in China, infants exposed to phototherapy for the treatment of hyperbilirubinemia, receive combination treatment with Chinese herbal medicine. This treatment results in lowered serum bilirubin levels and facilitates the recovery of jaundice [7]. In Iran, some researchers have also considered traditional medicine, especially the use of herbs. From ancient times, several herbs have been mentioned in popular medical books, such as the Law of Abu Ali Sina, Al-Hawi Razi, Al-Adawiyah Aghili Khorasani's Reservoir, and other valuable books [6]. For example, *Cotoneaster frigidus* is used in several regions of Iran to treat neonatal jaundice. *Cotoneaster frigidus* is a slightly yellowish-white sweet substance known as purgative manna. It is in the genus Cotoneaster of the family Rosaceae and the major constituents of which are carbohydrates including mannitol, fructose, glucose, and sucrose [11]. Some studies in this area have reported positive effects and some reported inefficacy of *Cotoneaster frigidus* on decreasing neonatal blood bilirubin levels [12, 13]. In a systematic review study (2016), alongside the positive effects of *Cotoneaster frigidus* in the treatment of neonatal jaundice, further studies on its mechanism of action have been suggested [14]. On the other hand, according to the results of another interventional study, the administration of *Cotoneaster frigidus* in the treatment of jaundice had no significant impact in comparison to placebo [15]. In another meta-analysis, although positive effects of *Cotoneaster frigidus* on neonatal jaundice were reported, it emphasized the need for further randomized clinical trials with larger sample sizes and controlled risk factors [16]. Thus, according to the results of previous systematic studies, and the suggestion of further investigations in this field plus the controversial findings obtained so far, the present study aimed to determine the effect of Bilineaster (*Cotoneaster frigidus)* oral drop on reducing the serum levels of bilirubin in neonates.

Materials and Methods

This randomized, triple-blind clinical trial investigated the effect of "Bilineaster" on physiological jaundice in neonates (IRCTID: IRCT2015120425203N2). This study was conducted on 96 neonates with physiological jaundice born in Dezful referring to pediatric clinic in 2018 and was approved by Dezful Medical Ethics Committee and registered in Iranian Registry of Clinical Trials as a triple-blind clinical trial (as the physician, researcher, statistician, and the family of neonates were not aware of any of the intervention and control groups). This trial compared the efficacy of routine therapy with oral placebo versus routine treatment with oral administration of Bilineaster manufactured by Sobhan Darou Co. The study population was randomly allocated into placebo and Bilineaster groups via a random allocation rule. The study population consisted of neonates with physiologic jaundice referring to Dezful Pediatric Clinic. The inclusion criteria were as follows: indication of phototherapy, term neonates (37-42 weeks), birth weight of 2.5 to 4 kg, and total serum bilirubin of 12-19 mg/d, breastfeeding, and the onset of jaundice after the second day. The exclusion criteria were all cases of conjugated hyperbilirubinemia, jaundice developed after 2 weeks, incompatibility of maternal and neonatal blood group and RH, any medical or traditional treatment, apparent physical abnormalities, decreased neonatal reflex strength, nutritional methods other than breastfeeding, hematocrit greater than 65% or hemoglobin greater than 20 g/dl, and abnormalities in blood testes (reticulocyte count above 5%, impaired glucose-6-phosphate dehydrogenase enzyme, positive Coombs test, positive blood smear for spherocytosis, ovalocytosis and Elliptocytosis), suggesting the presence of pathologic jaundice or underlying disease causing jaundice. In this study, first, the researcher explained the study protocol for the parents of eligible infants and if their infants were included in the study, they were randomly allocated to one of the two experimental and control groups. They were assured that not participating in the study would not cause any problem in their routine care and services, and thereafter informed consent was obtained. Then, the researcher enrolled a total of 96 neonates and allocated them into the experimental and control groups randomly. In addition to random allocation of the population,

which would increase the similarity of underlying confounder variables between the two groups, to ensure correct matching, several demographic characteristics and confounding variables were compared between the two groups at baseline. For this purpose, in addition to recording demographic characteristics (gender, type of delivery, weight, route of nutrition) and related records at baseline, to rule out potential problems blood samples were collected in order to determine total bilirubin, indirect bilirubin, percentage of reticulocyte count, hemoglobin, neonatal blood group, and RH, and for the diagnosis of G6PD deficiency. In the follow-up period and given the specific aims of the study as well as adhering to the ethical considerations of routine treatment, phototherapy, as the primary treatment, was performed for all neonates in the experimental and control groups. In the control group, phototherapy was also performed in combination with placebo. On the other hand, in the intervention group, phototherapy was administered in combination with the administration of Bilineaster drops. Serum levels of bilirubin were measured 0, 24, 48, 72 hours after the initiation of the intervention. The shape and packaging of the placebo were exactly the same as the Bilineaster drop provided by the pharmaceutical manufacturer by the commission of the placebo research group. For differentiating between the placebo and medication, special codes and the full name of patients on the packaging were used, where only one of the principal investigators who was not involved in the treatment process was aware of this. It should be noted that Bilineaster and placebo were administered for 72 hours and the bilirubin level was checked every day, and further compared and recorded. In addition, phototherapy was performed under the same conditions for all neonates. Phototherapy had 6 bulbs with a specific blue fluorescent light with wavelengths of 400 to 460 nm. The duration of phototherapy was based on indirect jaundice greater than 10 mg/dl and the patient's health status. The eyes and genital area of neonates were also covered with protective eye and genital shield during phototherapy. In this study, the experts in blood sampling, data recording, and evaluation of the results who were laboratory staff, pediatrician, and results analyzer, were not informed of the group to which the infants belonged, and only were aware of the patients' full name. Serum bilirubin levels were measured at baseline and every 24 hours by BRM-PLUS for baseline and 72 hours, and the Bili-Chek-PHILIPS for baseline and every 24 hours. In this study, the statistical analysis of bilirubin was performed using the Bili-Chek. There was no statistical difference between the results of bilirubin with both devices (p=0.84).

Sample size formula

$$N = \frac{2(Z1 - \frac{1}{2} + Z1 - \beta)\partial^2}{(\mu 1 - \mu 2)2} \quad (1)$$

In this study, the values of $\alpha = 0.01$, $\beta = 0.2$, $\text{ʊ} = 2.07$, $\mu 1 = 13.82$, and $\mu 2 = 12.23$ were considered, where the sample size was estimated to be 40 individuals in each group. Next, by considering the probability of 20% for the attrition rate, 48 individuals were determined in each group.

Bilineaster oral Drop (*Cotoneaster frigidus*)

Each milliliter of Bilineaster drop contains 300 mg mannitol (the active ingredient of *Cotoneaster frigidus*) and can be used as supplementary treatment in neonatal jaundice and similar cases with elevated levels of serum bilirubin.

The application method of Bilineaster Drop in this study: The infants were administered 3 drops of Biliy Naster (*Cotoneaster frigidus* manufactured by Sobhan Darou Company) per body weight unit every eight hours. Data were analyzed using SPSS software (Version 23). The normal distribution of data was confirmed by the Kolmogorov-Smirnov test. Descriptive statistics such as frequency, mean, standard deviation, and inferential statistics such as chi-square test, independent t-test, and ANOVA with repeated measures were used to analyze the data. At the time of admission, total bilirubin, direct bilirubin, G6PD, and complete blood tests were assessed at baseline. Also, the bilirubin levels were measured every 24 hours (24, 36, 48, and 72), and the results were compared between the groups by repeated measures of the analysis of variance, and Duncan's test. The analysis of variance was used to compare the bilirubin level between the groups at baseline and after the intervention.

Results and Discussion

The results of this study conducted from late 2016 to early 2018 showed that out of 96 neonates with physiological jaundice referring to Dezful pediatric clinic, 49 (53.8%) were boys and the rest were girls. Forty-eight (52.7%) of the neonates were born through normal delivery. The age range of our population was 2-10 days and their mean age was 4.8 ±1.5 days and their mean weight at the time of the disease was 3.021 ± 0.41 g. The results indicated that there was no significant difference in demographic and descriptive characteristics of patients (age, birth weight, and weight at onset of jaundice) between the two groups (gender (p=0.7), type of delivery (p= 0.09)); hence, it can be claimed that both groups were well matched at baseline **(Table 1)**.

Table 1. Comparison of the mean and standard deviation of the quantitative and qualitative variables between the experimental and control groups at baseline

Variables	Case	Control	P
Neonate age	5.01±1.3	4.6±1.7	0.5
Birth weight	3.148±498	3.181±502	0.4
Weight to start treatment	3.017±398	3.025±490	0.8
Hemoglobin	16.06±1.38	15.17±2.09	0.07
Mean reticulocyte count	1.72±1.22	1.45±1.38	0.4

During the study, five neonates (two in the experimental group and three in the control group) were excluded due to their parents' request. Since the attrition rate was estimated to be 20%

of the sample size in each group. This exclusion caused no particular problem with the sample size and the data for the excluded neonates were omitted. Kolmogorov-Smirnov test was used to compare the distribution of the collected data with a normal distribution. According to the collected data, the value of variables was not significant at the level of 0.05 (at time zero, p=0.098; at 24 hours, p=0.40; at 48 hours, p=0.060; at 72 hours, p=0.067). Thus, it can be concluded that the distribution of data related to the research hypotheses was normal and the assumption of the normality of data was confirmed, hence, we could use repeated measures ANOVA.

Moreover, other results related to the main purpose of the study revealed that there was no difference between the control and the experimental groups at time 0 and the subsequent 24 hours. However, at 48 and 72 hours after the initiation of the intervention, a significant difference was observed between the two groups, and a greater mean reduction of scores belonged to the Bilineaster group **(Table 2)**. In addition, the repeated measures analysis of variance indicated that there was a significant difference for the mean scores of the control group between time zero and 72 hours after initiation. This indicates that the effect of time on the data is considerable. Repeated measures analysis of variance in the experimental group also showed that there was a significant difference in the mean scores between the time zero and 72 hours after the initiation of the intervention, and the effect of time on the data was considerable, with a descending trend of the mean scores being clearly observed in the graph **(Figure 1)**. Finally, the repeated measures analysis of variance showed that there was a significant difference in the effect of time between the two study groups.

Table 2. Comparison of the mean and standard deviation (mean ± SD) between the control and experimental groups

Measuring time	Case	Control	Independent t-Test	Analysis of variance with repeated measures (intergroup)
0	16.39±0.71	16.35±0.96	t=0.251 p=0.80	F=15.93
24	14.13±0.76	14.45±0.93	t=1.77 p=0.08	p=0.001
48	12.03±0.91	12.61±0.97	t=2.94 p=0.004	
72	10.97±0.79	11.65±0.86	t=3.89 p=0.001	
Analysis of variance with repeated measures	F=207.31 p=0.001	F=269.001 p=0.001		

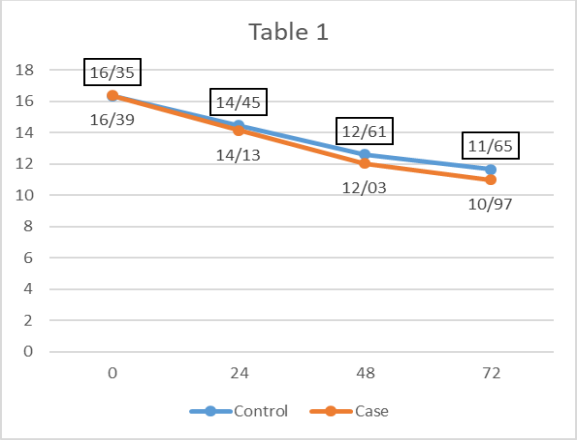

Figure 1. The trend of the mean reduction for bilirubin level in the control and experimental groups

These findings showed that Bilineaster (containing *Cotoneaster frigidus* as the main constituent) was effective in the treatment of neonatal jaundice; in combination with phototherapy, it caused more reduction in serum bilirubin level. In this regard, the clinical trial by Khoshdel showed that the administration of *Cotoneaster frigidus* (Bilineaster Drop) reduced neonatal jaundice more rapidly and also shortened the length of hospital stay [17]. Likewise, a similar study by Ghotbi showed that the administration of *Cotoneaster frigidus* reduced neonatal jaundice more rapidly and also decreased the length of hospital stay [18]. Again, Azadbakht reported a descending trend for bilirubin level in response to the consumption of *Cotoneaster frigidus* oral drop in comparison to the control group [19]. Rafatian found similar results in his study [6]. The mentioned studies showed results in line with the findings in the current trial. However, contrary to the results of these studies and the present study, Farhat observed that *Cotoneaster frigidus* (Bilineaster drop) had no effect on serum bilirubin level and this study showed no evidence for prescription of this medication in neonatal jaundice [20]. This inconsistency might be due to the low dose of the prescription, since in this study, neonates in the experimental group received only 6 g of *Cotoneaster frigidus* during the first hour of hospitalization. In the same vein, Reyhani found that the administration of *Cotoneaster frigidus* (Bilineaster) to neonates did not have any effect on the reduction of bilirubin level and the hospitalization duration, and this herbal medicine was not effective in the treatment of neonatal jaundice [21]. The inefficacy of *Cotoneaster frigidus* in reducing the bilirubin level in Reyhani study might be due to the short duration of intervention because of early discharge (earlier than 48 hours) of several neonates and a small sample size, which have been pointed as the limitations of the study. In the present study, the downward trend of bilirubin level in the intervention group was evident. Also, the results showed a difference in the extent of reduction in serum bilirubin level between the intervention and control groups, though the rate of bilirubin reduction was higher in the first two days than in the third day. In addition, Khoshdel emphasized the effect of time in reducing bilirubin levels, and reported a sharper descending trend for bilirubin level in the first 2 days than in the next 2 days, and explained its reason as the decrease in bilirubin level. It is because the higher the infant's bilirubin level, the more likely it is to be

affected by phototherapy and *Cotoneaster frigidus* consumption [17].

Bilineaster is produced from the aqueous extract of manna Purgative from the herb *Cotoneaster Discolor*. *Cotoneaster frigidus* contains mannitol, sucrose, dextrose, fructose, and multiple polysaccharides. The amount of mannitol in *Cotoneaster frigidus* is 40-60%. The absorption of oral mannitol in the gastrointestinal tract is very limited and may cause osmotic diarrhea in the intestine. This property of mannitol in *Cotoneaster frigidus* probably causes light-induced excretion of the optical and structural isomers of bilirubin or entering the intestine through the metabolic cycle through the stool, thus causing reduced serum levels of bilirubin. Khoshdel in his study described the mechanism of *Cotoneaster frigidus* (Bilineaster) as a consequence of the effect of mannitol, which results in bilirubin reduction by increasing excretion and decreasing the liver-intestine cycle. He also suggested another mechanism by which activating the hepatic receptor reduces the level of serum bilirubin [17]. In another study, Fakhri also identified mannitol as one of the main therapeutic compounds in *Cotoneaster frigidus*. According to Fakhrie's research, a very little amount of mannitol would be absorbed in the gastrointestinal tract, some of which would be excreted unmetabolized through the urine, and some metabolized to carbon dioxide in the liver. If mannitol is taken orally, it may cause osmotic diarrhea [22], due to slight absorption. However, Rafatian suggests the mechanism for the effect of *Cotoneaster frigidus* as increasing the excretion of bilirubin in feces without altering defecation frequency [6]. However, Ahmad shah *et al*. did not report any difference in the frequency of defecation in the two intervention and control groups [23]. Nevertheless, further research is required to determine the exact mechanism underlying the effect of Bilineaster (*Cotoneaster frigidus*) on the reduction of bilirubin level.

Conclusion

The results of the present study suggested that the administration of Bilineaster oral drop is effective in decreasing the level of bilirubin in neonates with jaundice undergoing phototherapy, and the consumption of this herbal medication over time leads to the increased slope of descending trend for bilirubin level changes. According to the results of the present study and some contradictory results from previous studies, meta-analysis and studies on the mechanism underlying Bilineaster's action, are recommended for further investigations on the prescription of this medication.

Acknowledgments: The authors would like to thank the vice-chancellor for the permission to carry out the research in Dezful University of Medical Sciences (Grant No: DUR-138. IR. /IRCTID: IRCT2015120425203N2) and would also like to thank the researchers for the financial support for the study as well as the participants who participated in this research.

Conflict of interest: None

Financial support: None

Ethics statement: None

References

1. Olusanya BO, Osibanjo FB, Mabogunje CA, Slusher TM, Olowe SA. The burden and management of neonatal jaundice in Nigeria: A scoping review of the literature. Niger J Clin Pract. 2016;19(1):1-7.
2. Huq S, Hossain SM, Haque SM, Tarafder MA. Knowledge Regarding Neonatal Jaundice Management among Mothers: A Descriptive Study Done In a Tertiary Level Hospital of Dhaka City. Anwer Khan Mod Med Coll J. 2017;8(2):121-7.
3. Maisels MJ. Managing the jaundiced newborn: a persistent challenge. CMAJ. 2015;187(5):335-43.
4. Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbesen F, et al. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. Pediatr Res. 2013;74(S1):86.
5. Nakanga W, Patel P, Panjwani S, Kennedy N, Kawaza K. Supra-treatment threshold neonatal jaundice: Incidence in HIV-exposed compared to non-exposed neonates at Queen Elizabeth Central Hospital in Blantyre, Malawi. Malawi Med J. 2015;27(3):104-8.
6. Rafieian-Kopaei M, Khoshdel A, Kheiri S, Shemian R. Cotoneaster: A safe and easy way to reduce neonatal jaundice. J Clin Diagn Res. 2016;10(4):SC01.
7. Wu RH, Feng S, Han M, Caldwell P, Liu SG, Zhang J, et al. Yinzhihuang oral liquid combined with phototherapy for neonatal jaundice: a systematic review and meta-analysis of randomized clinical trials. BMC Complement Altern Med. 2018;18(1):228.
8. Murki S, Kumar P. Blood exchange transfusion for infants with severe neonatal hyperbilirubinemia. InSeminars in perinatology 2011;35(3):175-84. WB Saunders.
9. Hamidi M, Aliakbari F. Comparison of Phototherapy with light-editing diodes (LED) and Conventional Phototherapy (fluorescent lamps) in Reducing Jaundice in Term and Preterm Newborns. Middle East J Family Med. 2018;7(10):123.
10. Zeng J, Wang SJ, Li YM, Li HS, Luo Q, Huang YY, et al. Yinzhihuang oral liquid in the treatment of neonatal jaundice: a meta-analysis. Pharm Biol. 2017;55(1):554-9.
11. Khodashenas E, Khakshour A, Momeni E, Sinaii M, Mir M. Systemic review of herbal medicine efficacy on neonatal Icterus. J North Khorasan Univ Med Sci. 2015;7(3):683-9.

12. Rafieian-Kopaei M, Khoshdel A, Kheiri S, Shemian R. Cotoneaster: A safe and easy way to reduce neonatal jaundice. J Clin Diagn Res. 2016;10(4):SC01.
13. Bakhshi Jouybari H, Hosseini AS, Davoodi A, Mirzaee F. Materia medica used in jaundice based on Persian medicine. Res J Pharmacogn. 2018;5(4):83-93.
14. Ostovar M, Marzban M, Salehi A. The effect of Cotoneaster manna on neonatal jaundice: A PRISMA-compliant systematic review. Planta Med. 2016;82(S 01):P961.
15. Shah Farhat A, Mohammadzadeh A, Ramezani MO, Amiri M. The effect of shirkhesht on newborns' indirect hyperbilirobinemia. Razi J Med Sci. 2005;12(47):93-8.
16. Salehi A, Ostovar M, Marzban M. A Systematic Review and Meta-Analysis on the Effect of Cotoneaster manna on Neonatal Jaundice. J Herb Drugs (An Int J Med Herbs).;9(1):47-54.
17. Khoshdel A, Kheiri S. Effect of shir-e-khesht (billinaster drop) consumption by the neonates or their mothers on the neonatal icter. J Shahrekord Uuniv Med Sci. 2011;13.
18. Ghotbi F, Nahidi S, Zangi M. Surveying the effect of cotoneaster spp.(shir khesht) on neonatal jaundice. Res Med. 2006;30(4):353-61.
19. Azadbakht M, Pishva N, Alinejad F. Effect of Manna from Cotoneaster discolor on infant Jaundice (effect on blood bilirubin level). J Med Plants. 2005;2(14):36-44.
20. Farhat AS, Mohammadzadeh A, Amir M, Ramezani M. Effect of cotoneaster tricolor pojark manna on serum bilirubin levels in neonates. Int J Pharmacol. 2006;2(4):455-8.
21. Rahani T, Boskabadi H, Sadeghi T, Boskabadi MH, Gharaei R, Pasban F. Comparison of the effect of cotoneaster manna drop (Bilineaster) and massage on bilirubin in neonates under phototherapy. J Babol Univ Med Sci. 2017;19(11):21-7.
22. Fakhri M, Davoodi A, Hamzegardeshi Z, Farhadi R, Mousavinasab N, Keshtkar A, et al. Is cotoneaster manna improving the treatment of neonatal jaundice?. Bangladesh J Pharmacol. 2018;13(2):168-78.
23. Farhat AS, Mohammadzadeh A, Amir M, Ramezani M. Effect of cotoneaster tricolor pojark manna on serum bilirubin levels in neonates. Int J Pharmacol. 2006;2(4):455-8.