

The effect of herbal medicine on neonatal jaundice: a systematic review

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Abstract

Background: Herbal remedies have been implicated as adjunctive therapies in the treatment of neonatal jaundice over the years. The aim of this review was to investigate the therapeutic effects of herbal medicines on neonatal jaundice.

Methods: In this systematic review, a search process was performed in online databases of Scopus, Medline, Web of Science and Cochrane Library based on PRISMA guidelines. Components for searching were “neonatal jaundice” and “herbal medicine”. Relevant articles in English published between January 1900 and October 2020 were extracted. The quality of the articles was assessed by the CONSORT checklist.

Results: Finally, according to the inclusion criteria, 9 studies with a total of 1323 neonates were selected. The herbal remedies used by the researchers for treatment of neonatal jaundice included Bilineaster drop, alhagi pseudoalhagi, and zizyphus jujuba were used in 8 of the 9 studies. In 5 of these 8 studies the Bilineaster (Purgative manna extract) had significantly reduced serum bilirubin levels of the infants.

Conclusion: Based on the results, the herbal remedies (especially bilineaster) are probability effective as adjuvant therapies along with standard therapies in the treatment of neonatal jaundice. These can reduce the bilirubin level – hospitalization days and re-hospitalization.

Key Words: Herbal medicine, Neonatal jaundice, Systematic review.

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1- INTRODUCTION

Jaundice appearing at birth or in the first 24 hours after birth is a pathologic condition which requires rapid management (1). Jaundice is a common and mostly benign finding with physiological or pathological patterns in the neonatal period (2, 3). During the first week after birth, jaundice is seen in 60% (4) and 80% (4, 5) of term and preterm infants, respectively. It is the most common cause of hospitalization in this period of life (6-8). Increased bilirubin has adverse effects on the brain (9). High indirect bilirubin deposits in the basal ganglia and brain stem nuclei and leads to neurological complications and kernicterus (bilirubin encephalopathy) (1). So, the most important goal of treatment is to prevent bilirubin-induced neurotoxicity (1).

There are some main and adjuvant therapies for neonatal jaundice that include phototherapy (10) exchange transfusion (11, 12), metalloporphyrins (13), intravenous immunoglobulin (IVIG) (7), clofibrate-laxatives (14, 15), ursodeoxycholic acid (16), massage, enema (17), and herbal remedies (18, 19). Phototherapy is the most common treatment for neonatal jaundice (7), but it can be associated with several complications including skin rash, loose stool, dehydration, hypothermia (20), overheating of the baby and bronze baby syndrome (1, 5). Phototherapy may be related to an excess in the risk of childhood cancer (21) and epilepsy in children (22, 23). Exchange transfusion is another treatment for neonatal jaundice when bilirubin reaches dangerous levels (1). Exchange transfusion can prevent many of the problems caused by increased jaundice, but it is costly and time consuming and may increase important morbidities and also mortality (24). On the other hand, the other treatments mentioned

also need to confirm their effectiveness and safety (25).

Herbal remedies have been implicated as adjunctive therapies in the treatment of neonatal jaundice over the years (6). These treatments have been used in China and India (26), Arabic countries (9, 24), Iran (6), and even European countries (27), for many years and are still used in combination with new jaundice treatments (28). In China, Yen Chen (*Artemisia Scoparia*) is the most common plant used for the treatment of neonatal jaundice (19) which is a traditional Chinese medicine and contains four plant extracts (29). On the other hand, some studies have shown that the use of traditional Chinese herbal medicine by the mother is also effective in reducing prolonged neonatal jaundice (2).

Nineteen plant species including *Acacia Catechu* Wild are used in the treatment of jaundice in traditional medicine in India (26). In Iran and South East Asian countries, plants such as *fumaria officinalis*, jujube, chicory, *Alhagi comelorum* and *cotoneaster* (*bilineaster-purgative manna*) have been used in the treatment of neonatal jaundice (9, 24). Purgative manna (*bilineaster drop*) is one of the most common herbal drugs in the management of jaundice in many parts of Iran (9, 30, 31). In addition, *Alhagi pseudoalhagi* is used for this purpose in some Central and Southern provinces of Iran (32).

Some review articles have been studied on the effect of herbal medicines on neonatal jaundice, but they are few in number and sometimes show conflicting results; the researchers have emphasized the need for more research in this area (6, 33). Using adjuvant therapies along with new therapies in the treatment of neonatal jaundice can improve therapeutic effectiveness and reduce jaundice complications. Also, due to low cost and availability of herbal medicines and the deep roots of herbal medicine in the

ancient knowledge of countries such as Iran, China and India, we decided to survey the therapeutic effects of herbal medicines on neonatal jaundice in a review study.

2- MATERIALS AND METHODS

This study was a systematic review that identified the effect of herbal drugs on neonatal jaundice and was designed based on Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines (34).

2-1. Eligibility criteria

The participants, interventions, comparators, and outcomes (PICO) were considered to formulate the review objective and inclusion criteria. Participants: Term and preterm (35-38) neonate. Interventions: Herbal medicine vs. other treatments. Comparators: Treatment vs. control group, treatment vs. different types of treatment, before vs. after treatment. Outcome: The primary and secondary outcomes.

2-1-1. Types of studies

Randomized Controlled trials (RCTs) and randomized trials studies with English language between January 1900 and October 2020 were eligible.

2-1-2. Types of participants

Infants were included if they were Healthy, under 14 days old, and had an increased bilirubin. Studies designed as letters to editor, editorials, commentaries, case reports or case series, and the reviews were excluded. Non-human clinical trials were also excluded.

2-1-3. Types of interventions

The experiments included a combination of phototherapy with one of the herbal medicines such as Bilineaster drop, or zizyphus jujuba, or alhagi pseudalhagi.

The control groups included the usual care (photography), or a combination of

phototherapy with Clofibrate, Glycerin, Placebo, or Massage.

2-1-4. Types of outcome measures

The primary outcomes dealt with the decrease in bilirubin levels and the secondary outcomes included the number of the neonate's hospitalization days, Frequency of hospitalization and Frequency of defecation.

2-2. Search Strategy

The components such as "Neonatal Jaundice" and "Medicine Herbal" were used for searching, along with their synonyms founded with Medical Subject Headings (Mesh). These topics were combined using the Boolean operators "AND" and "OR". The Search was conducted in databases PubMed/ Medline, ISI/Web of Science, Scopus, and the Wiley, from January 1900 to October 2020. The syntax is shown in **Appendix 1**. In addition, we used hand-searching in the references of the included studies to find the other related studies. After searching, all articles were entered to EndNote Reference Manager X8 and the duplicate articles were deleted.

2-3. Data extraction

The studies were, first, screened according to the inclusion criteria after reading their titles and abstracts. The approach for selecting the articles is visible in the PRISMA diagram (**Fig. 1**). The information that was extracted (Selected articles) included the name of the first author, publication year, research location, study design, sample size, primary and secondary outcomes, as well as the characteristics of herbal medicine treatment and control groups (**Table 1**). The information of the final articles was entered into a researcher-made checklist.

In this study, the decrease in bilirubin levels and the number of the neonates' hospitalization days were considered as primary and secondary outcomes,

respectively. Data extraction was done by two researchers and in case of disagreement, a third person resolved it.

2-4. Quality assessment

Quality assessment of the studies was conducted based on the Consolidated Standards of Reporting Trials (CONSORT) checklist (35). Each part of

the checklist was separated with a score between 0-2. Based on the total scores (score 74) obtained from the checklist, the article was classified as weak (scores <25), moderate (scores 25-48), or good (scores 49-74).

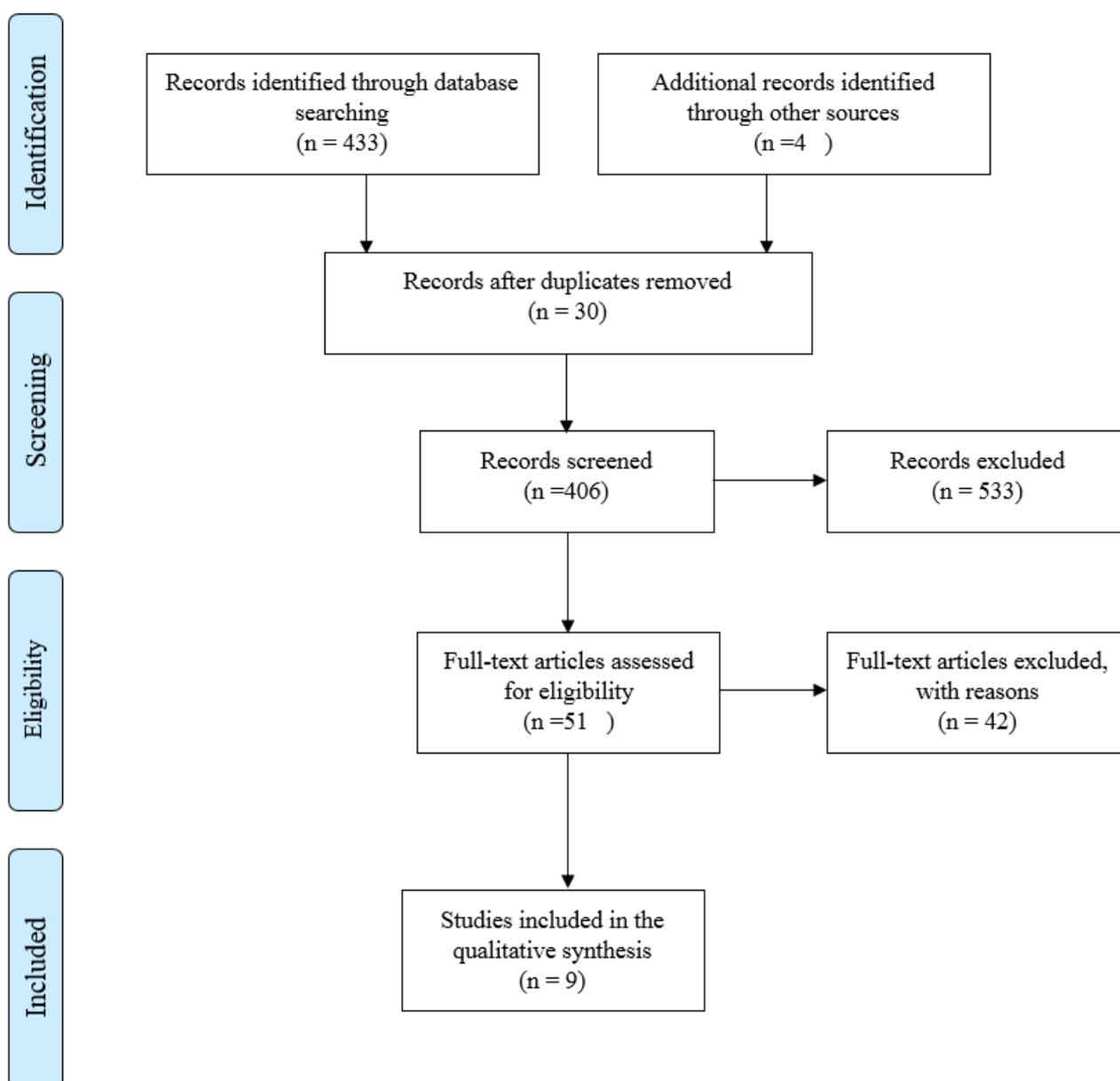


Fig. 1: PRISMA flow chart of the current study

Table-1: The general characteristics, Intervention and outcome measures of the included studies

Author, Year Country,(Reference)	Type of study/NG	Sample Size	Target population/ weight	Score	Trial group	Control group	Outcome		P-value	
							PO	SO	PO	SO
Rafieian Kopaei et al. 2016. Iran (38)	RCT/ 4groups	120	Term N/ 2.5-4 kg-	42	1. Mothers and neonates received Bil. 2. Mothers received Bil. 3. Neonates received Bil+Phototherapy	Neonates received distilled water +Phototherapy	Reduction of ISB	-	P < 0.05	-
Fallah R et al.2014. Iran (24)	SBRCT/ 3 groups	90	Term N / 2.5-4 kg-	48	1. Bil drop +phototherapy. 2. glycerin + phototherapy	Phototherapy	Reduction of ISB	H day	P<0.05	P<0.05
Mohammadi B et al.2020. Iran (32)	RCT/ 3groups	171	Term N / 2.5-4 kg-	40	1. PM + phototherapy. 2. alhagi pseudalhagi +phototherapy	Phototherapy	Reduction of ISB	-	P= 0.001	-
Monsef A et al. 2019. Iran (37)	DB RCT/ 2group	150	Term N/ 2.5-4 kg-	50	-PM drop +phototherapy	Phototherapy	Reduction of ISB	H day	P < 0.001	P = 0.06
Fakhri M et al. 2019. Iran (30)	DB RCT/ 2group	445	Term N / 2.5-4 kg-	62	-PM drop +phototherapy	droplet product +phototherapy	Reduction of ISB	F rehospital/ F defecation	P < 0.001	p<0.00 p<0.001
Ebrahimi S et al. 2011.Iran (39)	DB RCT/ 2group	121	Term N /C:3193±479gr, T: 3030±400 gr	32	ziziphus jujuba's fruit+phototherapy	distilled water +phototherapy	Reduction of ISB	H day/ F defecation	P =0.1	P 0.001
Mahyar A et al. 2019.Iran (36)	SBRCT/ 3group	60	Term N/ 2.5-4 kg-	49	1. Bil drop +phototherapy. 2. clofibrate+phototherapy	phototherapy	Reduction of ISB	H day/ Side effects	P.>0.05	P<0.05 P<0.05
Rahani T et al. 2017.Iran (9)	CT/ 3group	68	Term and Preterm (35-42) N wk /above 2 kg	44	1. Massage+phototherapy. 2.Bil drop +phototherapy	phototherapy	Reduction of ISB	F defecation	P= 0.4	P=0.65
Ameli Z et al. 2017.Iran (31)	RCT/ 2group	98	Term N/ above 2 kg	50	1. Bil drop +phototherapy 2. glycerin +phototherapy	phototherapy	Reduction of ISB	H day	P= 0.1	P< 0.001

Bil: Bilineaster; PM: Purgative manna; Reduction of ISB: Reduction of level serum bilirubin, H day: Hospitalization days; F rehospital: Frequency of rehospitalization; F defecation: Frequency of defecation; C: Control group. T: Trial group; RCT: Randomized clinical trial; CT: Clinical trial study; DB RCT: Double blind randomized clinical trial; SBRCT: Singles- blind randomized controlled clinical trial; Term N: Term neonates; Term and Preterm N: Term and Preterm neonates; PO: Primary outcome; SO: Secondary outcome; N G; Number of Group; S Size: Sample Size

3- RESULTS

Regarding the effect of herbal medicines on the treatment of neonatal jaundice, 436 studies were identified (electronic and manual) and 30 studies were eliminated due to duplication. After the preliminary review of the abstracts, 51 studies were selected and the other unrelated articles were removed. Finally 9 studies were evaluated based on the inclusion and exclusion criteria. The article selection process is shown in **Diagram 1**. According to the CONSORT quality assessment, three studies had good scores (30, 32, 36) and the rest had average scores (Table 1).

In the 9 finally selected studies, a total of 1,323 neonates were evaluated. Herbal medicines were used in 8 studies for the treatment and in one study they were used for the prevention of neonatal jaundice (**Tables 1**). 2 of the 9 clinical trial studies were double-blind randomized clinical trials (30, 37), and the rest were randomized clinical trials. The herbal remedies used for the treatment of neonatal jaundice included bilineaster drop (9, 24, 30-32, 37, 38), alhagi pseudalhagi (32), and zizyphus jujuba (39). In most of these studies, the samples were divided into three groups. The researchers prescribed phototherapy to the infants in the first group, a combination of phototherapy and one of the herbal medicines in the second group, and combination of phototherapy and Clofibrate (36), glycerin supp (24), placebo (30, 38) or massage (9), in the third group.

In the study of Fakhri et al. (2019), the effect of bilineaster drop on neonatal bilirubin level was investigated prophylactically. The difference between the intervention group (bilineaster drop) and control group (placebo) in terms of the mean total bilirubin levels after three days of treatment was 2.1 mg/dl ($p < 0.001$) in the experimental group (drop bilineaster) which was significantly different from the

decrease in the control group (placebo). The rate of defecation in the intervention group in the first, second and third days after treatment was 1-2 times more than the control group ($p < 0.001$) (30).

Monsef et al. (2019) examined the effect of bilineaster drops on bilirubin reduction in infants. They showed that at 48 and 72 hours after the treatment, the means of the direct and total bilirubin in the intervention group (bilineaster drop and phototherapy) were significantly lower than the control group (phototherapy only) ($P < 0.001$). But there was no statistically significant difference between the mean lengths of hospital stay between the two groups (37). In the study by Fallah et al. (2014), the infants were divided into three groups. The infants in the first and second groups received phototherapy, and phototherapy along with bilineaster drop, respectively. The infants in the third group received phototherapy with glycerin suppository. The level of total and direct bilirubin levels after 24 and 48 hours as well as the length of hospitalization of infants were significantly lower in the second and third groups in comparison to the first group ($P < 0.05$) (24).

Rafieian-kopaei et al. (2016) conducted a randomized clinical trial study with four groups. In the first and second groups, either the infants or the mothers received bilineaster drop, and in the third group, both of the mother and infant received the bilineaster drop, and in the fourth group, the infants received distilled water. In all groups, the infants also received phototherapy. The results of the study demonstrated that in the first, second and third groups, at 24 and 36 hours after the start of treatment, the level of direct and total bilirubin was significantly lower than the fourth group ($P < 0.05$) (38). Mohammadi et al. (2020) in a three groups randomized clinical trial study evaluated the effects of two herbal drugs bilineaster and Alhagi pseudalhagi in comparison to

phototherapy on reducing bilirubin levels in infants. They reported that Alhagi pseudoalhagi was significantly effective in reducing bilirubin levels compared to phototherapy; but the Bilineaster was not found to be effective (32). Mahyar et al. (2019) conducted a randomized clinical trial study to compare the effect of clofibrate and purgative Manna on hyperbilirubinemia in 60 neonates. In this study the samples were divided into three groups. The first group received phototherapy; the second group received phototherapy and purgative Manna and the third received phototherapy and Clofibrate. The results illustrated that there was no significant difference between groups in terms of bilirubin reduction in 24, 48 and 72 hours after the beginning of the intervention ($P > 0.05$). However, the rate of hospital stays in the second and third groups was significantly shorter than the first group ($P < 0.05$) (36).

Rahani et al. (2017) evaluated the effect of massage in reducing bilirubin in neonates in comparison to phototherapy. They measured direct and total bilirubin levels at 24, 48 and 72 hours after the start of treatment. There was no statistically significant difference between the three groups in the mentioned hours in terms of reduction of bilirubin levels in infants (9).

In a study by Ebrahimi et al. (2015) in Iran, 121 infants with elevated bilirubin levels were divided into control group (phototherapy and distilled water) and intervention group (phototherapy and *Zizyphus jujuba*). Bilirubin levels were assessed before the treatment, 12 hours after treatment and then every 24 hours of treatment till discharge time. At the 12th hour after the treatment, bilirubin levels in the intervention group were significantly lower than the control group ($P < 0.01$). However after three days, bilirubin levels were not significantly different between the two groups ($P = 0.1$). Also, the duration of hospitalization in the

intervention group was not significantly different from the control group (39).

4- DISCUSSION

This review study evaluated the effects of herbal remedies on neonatal jaundice. In 8 of the 9 finally selected clinical trial studies, phototherapy was used as the standard treatment to reduce bilirubin. In 8 out of 9 studies (9, 24, 30-32, 36-38) Bilineaster or cotoneaster drop (derived from purgative manna) was one of the drugs or the only drug used to evaluate its effects on neonatal jaundice. The other drugs or therapeutic measures used in these clinical trial studies included Alhagi pseudoalhagi drop (32), glycerin suppository (24), massage (9), clofibrate (36) and *Zizyphus jujube* (40). From among the 8 studies using Bilineaster drop (purgative manna), 4 studies (30, 31, 37, 38) only used this drug, and its effects were compared to phototherapy alone or to the placebo group. In these 4 studies, positive effects of Bilineaster drop were seen in reducing neonatal jaundice and in two studies (31, 38) a reduction in hospitalization days was also observed.

In Rafieian- Kopaei's et al study, simultaneous use of Bilineaster drop by the mother and infant was more effective than taking it separately by either the mother or the infant (38).

This indicates that Bilineaster is also secreted from breast milk and in this way, it may also reduce neonatal jaundice. Also, Ameli et al. showed that using Bilineaster drop in neonates with jaundice reduces their re-hospitalization. For this purpose they evaluated the therapeutic effects of Bilineaster one month after discharge from the hospital by calling the mothers (31). So it is suggested to follow-up the neonates who have received Bilineaster after discharge from hospital. In the study by Fallah et al., it was found that the effects of glycerin suppository in reducing neonatal jaundice was more than

Bilineaster drop (86.7% vs. 73.3%); although the Bilineaster drop in reducing neonatal jaundice has been effective and safe (24).

However, in contrast to these studies showing positive effects of Bilineaster on reducing neonatal jaundice, three other studies (9, 32, 36) reported that Bilineaster drop had no effect on the treatment of neonatal jaundice. In the study by Mohammadi et al. (2020), neonates receiving the Alhagi drop had significantly lower mean bilirubin levels compared to those who received Bilineaster drop and the control group; their results confirmed no effect for the Bilineaster drop on the treatment of neonatal jaundice (32). Rahani's et al study, likewise, revealed that using massage and Bilineaster drop had no effect on reducing bilirubin in infants under phototherapy (9). Also, in the study by Mahyar et al, Bilineaster drop and Clofibrate were found to have no effect on reducing bilirubin in the infants under phototherapy (36).

According to the reviewed studies, it seems that the Bilineaster drop is the most widely used herbal remedy in the treatment of neonatal jaundice in Iran. Two mechanisms in Bilineaster can lead to the reduction of jaundice (36). The first mechanism is attributed to mannitol which forms 40%-60% of Bilineaster. Mannitol increase bilirubin excretion can be effective through stool by causing osmotic diarrhea and increasing the frequency of stools (32, 36). Activating the hepatic receptors is the second mechanism of Bilineaster which leads to increased bilirubin clearance via kidneys (36). Other drugs or therapeutic measures used in these clinical trial studies included glycerin suppository (24), Alhagi pseudoalhagi drop (32) zizyphus jujuba extract (40) and massage (9).

Due to the rich scientific history of Iran and the existence of rich sources of traditional medicine and great scientists in

the past, it is expected that many of the studies on the effects of herbal medicines on reducing neonatal jaundice be conducted in Iran. On the other hand, Iranian researchers in a country like Iran with four seasons of the year, extensive climatic diversity, the growth of various medicinal plants, and a long history of using herbal medicines, in respect to the side effects of chemical drugs can suggest less risky treatments with herbal remedies for infants. Studies have been done in other ancient countries such as China and India. However, most of them were review or descriptive articles and were not selected for this study. Of course, there have been several Chinese clinical trials, but they were published in the Chinese journals, and their full text was not available in English.

4-1. Limitations of the study

Among the limitations of the study was the limited number of clinical trial studies on the treatment of neonatal jaundice with herbs and their being exclusive to a few countries. On the other hand, the variety of herbs used in the treatment of neonatal jaundice has been limited.

5- CONCLUSION

This systematic review showed that the herbal remedies (especially Bilineaster drop) are probably effective as adjuvant therapies along with standard therapies in the treatment of neonatal jaundice. These can reduce bilirubin level – hospitalization days and re-hospitalization. So, herbal remedies can reduce the cost of hospitalization and also decrease complications of phototherapy and exchange transfusion. Thus, clinical trial studies with larger sample sizes and also studies on the herbal remedies other than Bilineaster are suggested

6- CONFLICT OF INTEREST

None.

7-AUTHORS' CONTRIBUTIONS

All authors contributed in designing, running, and writing all parts of the research.

8- FUNDING

This study did not have any financial supporters.

9- ETHICAL CONSIDERATIONS

This study was a systematic review and uses the results of the previously published studies, so no ethical approval or patient consent was required.

Appendix.1: Search strategy in data bases (PubMed, Web of Science, Scopus, and the Wiley)

SCOPUS syntax:

ALL("Herbal medicine") OR ALL(Bilineaster) OR ALL("Purgative Manna") OR ALL(Yin Zhi Huang) AND ALL("Neonatal jaundice") AND (PUB YEAR > 1990 AND PUB YEAR < 2021) OR PUBDATE TEXT(October 2020)

Result search in Scopus: 182

WEB OF SCIENCE syntax:

(TS=("Herbal medicine") OR TS=(Bilineaster) OR TS=("Purgative Manna") OR TS=(Yin Zhi Huang)) AND TS=("Neonatal jaundice") AND PY=(1990-2020)

Result search in web of science: 13

PubMed syntax:

("Herbal medicine" OR Bilineaster OR "Purgative Manna" OR Yin Zhi Huang AND "Neonatal jaundice") AND 1990/01/01:2020/10/30[dp]

Result search in PubMed: 22

WILLEY syntax:

"Herbal medicine" OR Bilineaster OR Purgative Manna OR Yin Zhi Huang AND "Neonatal jaundice" AND 1990:2020

Result search in Willey: 215

10- REFERENCES

1. Martin RJ, Fanaroff AA, Walsh MC. Neonatal-perinatal medicine: diseases of the fetus and infant: Elsevier/Mosby St Louis; 2011.
2. Weng Y-H, Chiu Y-W, Cheng S-W. Breast milk jaundice and maternal diet with Chinese herbal medicines. Evidence-based complementary and alternative medicine: eCAM. 2012; 2012.
3. Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. New England Journal of Medicine. 2001; 344(8):581-90.
4. Chou S-C, Palmer RH, Ezhuthachan S, Newman C, Pradell-Boyd B, Maisels MJ, et al. Management of hyperbilirubinemia in newborns: measuring performance by using a benchmarking model. Pediatrics. 2003; 112(6):1264-73.
5. Mukherjee D, Coffey M, Maisels M, editors. How many babies in the NICU receive phototherapy and for how long? ACTA PAEDIATRICA; 2017: WILEY

111 RIVER ST, HOBOKEN 07030-5774, NJ USA.

6. Fakhri M, Farhadi R, Mousavinasab SN, Yosefi SS, Hosseinimehr SJ, Azadbakht M. Effect of natural products on jaundice in Iranian neonates. *Jundishapur J Nat Pharm Prod*, online ahead of print. 2019; 14:e83042.

7. Mreihil K, Benth JŠ, Stensvold HJ, Nakstad B, Hansen TWR, Group NNPS, et al. Phototherapy is commonly used for neonatal jaundice but greater control is needed to avoid toxicity in the most vulnerable infants. *Acta Paediatrica*. 2018; 107(4):611-9.

8. Kianmehr M, Moslem A, Moghadam KB, Naghavi M, Noghabi SP, Moghadam MB. The effect of massage on serum bilirubin levels in term neonates with hyperbilirubinemia undergoing phototherapy. *Nautilus*. 2014; 128:36-41.

9. Rahani T, Boskabadi H, Sadeghi T, Boskabadi M, Gharaei R, Pasban F. Comparison of the effect of cotoneaster manna drop (Bilineaster) and massage on bilirubin in neonates under phototherapy. *Journal of Babol University of Medical Sciences*. 2017; 19(11):21-7.

10. Chu L, Xue X, Qiao J. Efficacy of Intermittent Phototherapy versus Continuous Phototherapy for Treatment of Neonatal Hyperbilirubinemia: A Systematic Review and Meta-analysis. *Journal of Advanced Nursing*. 2020.

11. Wolf MF, Childers J, Gray KD, Chivily C, Glenn M, Jones L, et al. Exchange transfusion safety and outcomes in neonatal hyperbilirubinemia. *Journal of Perinatology*. 2020:1-7.

12. Duan L, Gan S, Hu H. A single-center experience on exchange transfusion therapy in 123 full-term cases of severe neonatal hyperbilirubinemia in Wuhan. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2020:1-7.

13. Stevenson DK, Wong RJ, editors. *Metalloporphyrins in the management of neonatal hyperbilirubinemia*. *Seminars in Fetal and Neonatal Medicine*; 2010: Elsevier.

14. Zahedpasha Y, Ahmadpour-Kacho M, Hajiahmadi M, Naderi S, Kamali AA. Efficacy of clofibrate on severe neonatal jaundice associated with glucose-6-phosphate dehydrogenase deficiency (a randomized clinical trial). *Southeast Asian journal of tropical medicine and public health*. 2008; 39(3):557.

15. Badeli HR, Sharafi R, Sajedi SA. The effect of clofibrate on neonatal hyperbilirubinemia in uncomplicated jaundice. 2008.

16. Gharehbaghi MM, Sani AM, Refeey M. Evaluating the effects of different doses of ursodeoxycholic acid on neonatal jaundice. *The Turkish journal of pediatrics*. 2020; 62(3):424-30.

17. Abdellatif M, Vuong NL, Tawfik GM, Elfaituri MK, Mansour MIM, Zaki MMM, et al. Massage therapy for the treatment of neonatal jaundice: A systematic review and network meta-analysis. *Journal of Neonatal Nursing*. 2020; 26(1):17-24.

18. Yu Z, Han S, Guo X, Gao C, Ji C. Chinese herbal medicines for the treatment of neonatal jaundice. *Cochrane Database of Systematic Reviews*. 2020; 2020(6).

19. Wu R-h, Feng S, Han M, Caldwell P, Liu S-g, Zhang J, et al. Yinzhihuang oral liquid combined with phototherapy for neonatal jaundice: a systematic review and meta-analysis of randomized clinical trials. *BMC complementary and alternative medicine*. 2018; 18(1):228.

20. Karakukcu C, Ustidal M, Ozturk A, Baskol G, Saraymen R. Assessment of DNA damage and plasma catalase activity in healthy term hyperbilirubinemia infants receiving phototherapy. *Mutation Research/Genetic Toxicology and*

- Environmental Mutagenesis. 2009; 680(1-2):12-6.
21. Wickremasinghe AC, Kuzniewicz MW, Grimes BA, McCulloch CE, Newman TB. Neonatal phototherapy and infantile cancer. *Pediatrics*. 2016; 137(6).
22. Newman TB, Wu YW, Kuzniewicz MW, Grimes BA, McCulloch CE. Childhood seizures after phototherapy. *Pediatrics*. 2018; 142(4).
23. Maimburg RD, Olsen J, Sun Y. Neonatal hyperbilirubinemia and the risk of febrile seizures and childhood epilepsy. *Epilepsy Research*. 2016; 124:67-72.
24. Fallah R, Ali Fallahzadeh M, Noori-Shadkam M. Evaluation of safety and efficacy of purgative manna (billinaster drop) and glycerin suppository in icterus of healthy term newborns. *Current drug safety*. 2014; 9(1):29-33.
25. Ameli Z, Assarroudi A, Akrami R. Effect of Bilineaster drop on neonatal hyperbilirubinemia. *Evidence Based Care*. 2017; 6(4):66-73.
26. Badgajar SB, Patil MB. Ethnomedicines for jaundice used in tribal areas of North Maharashtra. *Indian Journal of Natural Products and Resources*. 2008; 7(1):79-81.
27. Yeung C, Leung C, Chen Y. An old traditional herbal remedy for neonatal jaundice with a newly identified risk. *Journal of paediatrics and child health*. 1993; 29(4):292-4.
28. Fok TF. Neonatal jaundice—traditional Chinese medicine approach. *Journal of Perinatology*. 2001; 21(1):S98-S100.
29. Yin J, Wennberg RP, Miller M. Induction of hepatic bilirubin and drug metabolizing enzymes by individual herbs present in the traditional Chinese medicine, yin zhi huang. *Developmental pharmacology and therapeutics*. 1993; 20:186-94.
30. Fakhri M, Farhadi R, Mousavinasab N, Hosseinimehr SJ, Yousefi SS, Davoodi A, et al. Preventive effect of purgative manna on neonatal jaundice: A double blind randomized controlled clinical trial. *Journal of ethnopharmacology*. 2019; 236:240-9.
31. Ameli Z, Assarroudi A, Akrami R. Effect of Bilineaster drop on neonatal hyperbilirubinemia. *Evidence Based Care Journal*. 2017; 6(4):66-73.
32. Mohammadi B, Daliri A, Sadeghi H, Mohammadi J. Comparison of the Effect of Purgative Manna and Alhagi Pseudalhagi Usage on Healing Icterus of Infants. *Journal of Clinical Care and Skills*. 2019; 1(2):89-93.
33. 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. *Pharmaceutical Biology*. 2017; 55(1):554-9.
34. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009; 62(10):e1-e34.
35. <http://www.consort-statement.org/consort-2010>.
36. Mahyar A, Mehrpisheh S, Khajeh B, Ayazi P, Oveisi S, Mahyar S, et al. The Effect of Purgative Manna and Clofibrate on Neonatal Unconjugated Hyperbilirubinemia. *Acta Medica Iranica*. 2019.
37. Monsef A, Eghbalian F, Rahimi N. Comparison of purgative manna drop and phototherapy with phototherapy treatment of neonatal jaundice: A randomized double-blind clinical trial. *Osong public health and research perspectives*. 2019; 10(3):152.

38. Rafieian-Kopaei M, Khoshdel A, Kheiri S, Shemian R. Cotoneaster: A safe and easy way to reduce neonatal jaundice. *Journal of clinical and diagnostic research: JCDR*. 2016; 10(4):SC01.
39. Ebrahimimd S, Ashkani-Esfahani S, Poormahmudibs A. Investigating the efficacy of *Zizyphus jujuba* on neonatal jaundice. *Iranian Journal of Pediatrics*. 2011; 21(3):320.
40. Nassirian H, Eslami ST. Effects of *cichorium intybus* on bilirubin. *Indian J Pediatr*. 2008; 75(4):331-3.