Review Article

http://wjpn.ssu.ac.ir

The Mechanism of Action of Cotoneaster Manna, an Iranian Herbal Medicine, in the Treatment of Neonatal Jaundice

Hossein Neamatzadeh[1,2], Sedigheh Ekraminasab[1,3*], Reza Bahrami[4], Fatemeh Asadian[5]

[1] Mother and Newborn Health Research Center, Shahid Sadoughi Hospital, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Department of Medical Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Department of Hematology and Blood Banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4] Neonatal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[5] Department of Medical Laboratory Sciences, School of Paramedical Science, Shiraz University of Medical Sciences, Shiraz, Iran

Received: 20 September 2023 **Revised:** 05 October 2023 **Accepted:** 25 October 2023

ARTICLE INFO

Corresponding author:
Sedigheh Ekraminasab

Email:
s.ekraminasab@gmail.com

Keywords:
Jaundice;
Bilirubin;
Purgative manna;
Infant;
Oxidants;
Phototherapy

ABSTRACT

Background: Neonatal jaundice is a common clinical problem caused by the deposition of bilirubin in the tissue. Natural products have long been used to treat jaundice, and Iranian medicine can be a good source of natural treatments for this purpose. In this study, we investigate the mechanism of the effect of Cotoneaster, an Iranian herbal medicine, in the treatment of jaundice in neonates.

Methods: We investigated every article that evaluated Purgative manna, Cotoneaster manna, or Cotoneaster in the treatment of neonatal jaundice. We searched the databases of PubMed, Scopus, Web of Sciences, SciELO, CNKI, and Google Scholar for English articles, and a search was also done in Persian in Magiran and Scientific Information Database (SID) published until August 2023.

Results: The exact mechanism of Cotoneaster in reducing jaundice is not known, but the following mechanisms have been suggested .The most common mechanisms include increased urination, increased bile excretion from the liver, and increased defecation, as well as neutralizing the effects of oxidative agents and free radicals.

Conclusion: Considering that most studies have stated that Cotoneaster combined with phototherapy is effective in treating jaundice and herbal medicines alone cannot treat jaundice. Therefore, identifying the mechanism of Cotoneaster in reducing jaundice can lead to the creation of methods to strengthen its effect. More detailed biochemical and pharmacological studies are needed to understand the mechanism of action of Cotoneaster in reducing neonatal jaundice.

Introduction

Jaundice is common in infants and is the most common cause of hospitalization.[1] Neonatal Hyperbilirubinemia is the yellowish discoloration of the sclera, skin, and mucous membranes caused by bilirubin deposition.[2] In severe cases, jaundice can damage the neonate's brain. In cases where the brain barrier is damaged, increased serum bilirubin levels can damage brain cells, especially the hippocampus, and brain nuclei, and lead to kernicterus.[3] There are several ways to treat Jaundice, including blood transfusions, phototherapy, and Medicinal agents. Any of these may have adverse consequences. Despite the promising results of blood exchange and phototherapy for hyperbilirubinemia, there are reports of dehydration, corona infliction, bronze baby syndrome, impaired reproductive organs, diarrhea, and risky adverse effects like apnea or thrombocytopenia.[4,5,6] Finding new methods to reduce the duration of treatment is one of the main concerns. In this regard, herbal medicines have recently been proposed as a new management strategy to reduce bilirubin levels.[6] Availability, acceptability, and affordability are also important points for such a survey.[7] In the past years, natural treatments, especially medicinal herbs, have been considered as side therapy in the treatment of jaundice. Many of the raw materials of these treatments are also used in the pharmaceutical industry.[3] These treatments include prescribing less absorbent foods such as herbal products, the most important of which are Cotoneaster (Shire khesht) and Alhagi maurorum Medik (Taranjebin).[3]

In terms of traditional medicine, due to its cold nature, many plants are used to treat jaundice by people and healers. These plants and their compounds reduce bilirubin in neonatal jaundice by different mechanisms.[8] Increasing the enterohepatic circulation and the activity of liver enzymes are among the mechanisms that have received more attention. Some plants directly degrade bilirubin and reduce serum bilirubin levels. Increasing the frequency of urination and defecation, which reduces intestinal-hepatic blood circulation, is another mechanism that has been specially considered for the use of Ziziphus jujube fruit.[9] Cotoneaster is a yellowish-white substance that is obtained from the gum of a tree called purgative manna of the Rosaceae family. Ethnobotanical studies in Iran have shown that the use of low doses of Cotoneaster manna in mothers or newborns can be effective in treating jaundice in newborns.[9] In addition, Khoshdel et al's study showed that the use of Cotoneaster along with the usual method can help reduce indirect bilirubin and shorten hospital stays.[10] Since the most common herbal medicine in reducing jaundice in neonates is Cotoneaster, this review study aims to investigate the mechanisms of action of Cotoneaster manna in reducing jaundice in neonates.

Herbal medicines in the treatment of infant jaundice

Several studies have been conducted on medicinal plants used to treat jaundice. Based on ethnobotanical evidence, six plant species from five families consisting of Ziziphus jujube Miller, Cotoneaster discolour, Fumaria parviflora, Alhagi graecorum Boiss, Chicorium, and intybus Hordeum vulgare, have been reported to be used to treat neonatal jaundice in Iran.[9,11] Today, Cotoneaster manna is widely used in Iran. In addition, many clinical trials have suggested Cotoneaster manna as a good choice in the treatment and prevention of neonatal Jaundice.[12] However, a combination of two or more of these herbs has been reported to treat neonatal jaundice. Although herbs and their compounds with different mechanisms of action reduce jaundice in neonates, in most cases they cannot be considered as an independent treatment. In the studies conducted, the use of plants and their compounds to reduce bilirubin has been recommended as a complementary treatment.[9]

Cotoneaster

Cotoneaster manna is a sweet yellowish-white substance known as Purgative manna. It is a mild laxative that removes toxins from the liver, bile ducts, gall bladder and stomach and is the best medicine for patients with fever. Cotoneaster is used in many regions of Iran, including Khorasan, Fars, and Lorestan, as a traditional medicine to treat jaundice in neonates.[3] Several studies have shown that the use of Cotoneaster by mothers and infants can lead to a reduction in bilirubinemia in infants.[13,14] Based on the available evidence, Cotoneaster can be recommended as a standard product alongside phototherapy to reduce neonatal jaundice, and pharmacists should consider it.[9]

Bilineaster

Bilineaster solution is a purgative manna extract from the Cotoneaster isocolor plant. Each milliliter of this herbal medicine contains 300 mg of mannitol. This drug is administered orally and is absorbed in a small amount from the digestive tract, which leads to osmotic diarrhea and helps to eliminate the different isomers of bilirubin.[15] According to the studies, Bilinaster drops are the most widely used herbal medicine in the treatment of infant jaundice in Iran. There are two possible mechanisms for the reduction of jaundice by Bilineaster drops. The first mechanism is attributed to mannitol, which constitutes 40-60% of Bilineaster. Mannitol causes osmotic diarrhea and increased stool frequency, thus increasing the excretion of bilirubin through the stool. The second mechanism of Bilineaster is the activation of liver receptors, which leads to increased clearance of bilirubin through the kidneys.[16]

Possible side effects of herbal medicines

The safety of medicinal herbs and low side effects have convinced many families to use these traditional and natural treatments to maintain their physical and mental health and treat diseases that affect their infants in the first two years of life.[17] According to studies by Rafieian-Kopaei, et al., Fakhri, et al., and Fallah et al., Cotoneaster had no major side effects.[14,18-20] Because Cotoneaster has a laxative effect, there is a theoretical concern that Cotoneaster manna may cause dehydration in infants by increasing bowel movements.[18]

Components

Cotoneaster manna is the most important component of Cotoneaster species, which produces a sweet source of manna.[21] Cotoneaster contains various carbohydrates and its main components are mannitol, glucose and sucrose.[14] In some types of manna, there are various other compounds such as phenolic compounds, flavonoids and essential trace elements that have different effects on the human body. Chemical compounds of Cotoneaster species were analyzed by HPLC, which were ruin, ursolic acid, chlorogenic acid and hyperoised.[19] These phenolic compositions have excellent antioxidant activity that protects liver cells against oxidative stress. Treatment with ursolic acid decreased serum aminotransferase activity and total bilirubin level in rats. Chlorogenic acid is able to reduce aspartate aminotransferase, alanine transaminase, alkaline phosphatase, direct bilirubin, total bilirubin, and total bile acid.[19]

Mechanism action of Cotoneaster manna

The mechanism of reducing bilirubin has not yet been proposed for cottonseed, but it has been confirmed that this herbal compound causes the excretion of bilirubin through the stool and thus reduces jaundice of the neonates.[14] But some other plants, such as H. vulgare, due to the presence of antioxidant phenolic compounds, reduce oxidative stress biomarkers and increase antioxidant biomarkers, and as a result, stop harmful tissue and biochemical changes in the liver and regulate the activity of liver enzymes.[22] In fact, natural compounds such as medicinal plants with their antioxidant activity can reduce oxidative stress and prevent many diseases.[9]

The most comprehensive research on the mechanism of Cotoneaster was done by Fakhri et al., in 2019.[19] we described four possible mechanisms. In previous studies and scientific sources such as Persian medical texts, the multiple functions of Cotoneaster in reducing the jaundice of newborns have been discussed according to its various compounds.

1. The laxative effect of Cotoneaster manna can lead to an increase in intestinal transit and the excretion of more bilirubin in the digestive system of infants to reduce the liver-intestinal cycle.[23,14]

2. Mannitol is the main source of sugar in Cotoneaster manna and helps reduce bilirubin in the digestive tract of newborns by inducing mild diarrhea.[24]

3. The binding of some Cotoneaster compounds with bilirubin prevents the reabsorption of bilirubin in the intestinal-hepatic circulation and reduces the bilirubin in newborns.[25,19]

4. Flavonoids in Cotoneaster manna may affect bilirubin metabolism and reduce bilirubin levels by antioxidant activity.[9] Considering that the antioxidant activity of Cotoneaster fruits and leaves largely depends on the content of polyphenols such as flavonoids, caffeoylquinic, acids and procyanidins, these plant compounds play an important role in their antioxidant capacity.[21]

It is generally assumed that sugar alcohols (especially mannitol) prevent the reabsorption of bilirubin through the intestine and excretion through the feces by affecting the liver cycle. Another part of the decrease in bilirubin level caused by the reduction of Cotoneaster can be attributed to the antioxidant effects of flavonoid compounds present in Cotoneaster. More detailed evaluations are needed for the therapeutic and laxative effects of Cotoneaster.[19] More detailed physicochemical studies are needed to determine the mechanism of action of Cotoneaster compounds.

Discussion

Hyperbilirubinemia is one of the most common problems seen in newborns and appears in the first week of birth.[26] Jaundice may cause serious complications such as kernicterus and lifelong disability.[27] Herbal medicines have recently received special attention in the search for bilirubin-lowering substances.[11] Rezapour et al., in a systematic review, evaluated the effect of herbal medicine on neonatal jaundice. Based on their results, Herbal medicines (especially Bilineaster) are most likely to be effective as adjunctive therapy along with standard treatments in the treatment of infant jaundice. These can lower bilirubin levels - days of hospitalization and re-hospitalization.[16] The use of medicinal plants as preventive or protective agents is a topic that has emerged in the current literature from traditional systems such as Iranian medicine.[6] Salehi et al., in a systematic review and Meta-Analysis evaluated the effect of Cotoneaster manna on neonatal jaundice. Their meta-analysis showed the positive effect of Cotoneaster manna on the treatment of neonatal jaundice.[28] Fakhri et al., assessed the preventive effect of purgative manna on neonatal jaundice. Cotoneaster (Shire Khesht) is most popular in Persian medicine. The various effects of some Cotoneaster species manna include antioxidant, antibacterial, liver protection effects, and anticancer, as well as reducing serum bilirubin levels. Cotoneaster manna is used as a laxative in many parts of Iran and accelerates the passage of meconium. Neonatal jaundice has relatively expensive and sometimes invasive therapeutic interventions, and prevention of turning into severe cases can be one of the priorities of neonatal medicine.[19]

The mannitol in Cotoneaster probably induces the photoexcretion of optical and structural isomers of bilirubin or enters the intestine by the metabolic cycle through feces, thereby reducing serum bilirubin levels.[29] In his study, Khoshdel stated that the mechanism of Bilineaster is the result of the effect of mannitol, which leads to a decrease in bilirubin by decreasing the liver-intestinal

cycle and increasing excretion. He also proposed another mechanism that lowers serum bilirubin levels by activating the hepatic receptor.[10] Fakhri et al., also identified mannitol as one of the main therapeutic compounds in Cotoneaster. According to Fakhri's study, a very small amount of mannitol is absorbed in the digestive system, part of which is excreted without metabolism through the urine, and some is metabolized to carbon dioxide in the liver.[30] However, Rafian Kopaei et al., suggested the mechanism of action of Cotoneaster as an increase in the excretion of bilirubin in the stool without changing the frequency of defecation. [14] But, Ahmad shah et al., did not report a difference in the frequency of defecation in the intervention and control groups.[29]

In general, there are various herbal medicines around the world to treat jaundice in neonates. Different mechanisms of action have been proposed for them, including activation of liver receptors that cause bilirubin clearance.[14] The exact mechanism of action of Cotoneaster manna is not known. Further research is needed to determine the exact mechanism of the role of Cotoneaster manna in reducing bilirubin.

Conclusion

According to Persian medicine, Cotoneaster manna causes the excretion of bile from the liver and gall bladder and shows the mechanism of Cotoneaster manna in reducing serum bilirubin levels. In addition, the main compound of Cotoneaster manna is mannitol, which produces the most therapeutic effects. These traditional medicine measures help to understand the mechanism of the effective effect of Cotoneaster manna in the treatment of newborn jaundice. These data may provide a basis for starting the search for new compounds related to pharmacology, phytochemistry, and pharmacogenetics. Also, this can be considered in the development of new drugs in the future. However, the exact mechanism of Cotoneaster manna has not been investigated and further study is recommended to evaluate the mechanism.

Conflict of Interest

Authors have no conflict of interest.

Acknowledgments

The authors thank the editors and the anonymous reviewers for insightful suggestions on this study.

Funding

No funding has been received for this study.

Ethical Considerations

None.

Author's Contribution

H.N. and S.E. conceived of the presented idea. R.B. and F.A. developed the theory. H.N. encouraged S.E., R.B. and F.A.to investigate the mechanism of the effect of Cotoneaster manna in the articles and texts of Iranian herbal medicine. Also S.E. supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

How to Cite: Neamatzadeh H, Ekraminasab S, Bahrami R, Asadian F. The Mechanism of Action of Cotoneaster Manna, an Iranian Herbal Medicine, in the Treatment of Neonatal Jaundice. World J Peri & Neonatol 2023; 6(1): 49-55.
DOI: 10.18502/wjpn.v6i1.14252

References

1. Ekraminasab S, Manzourolhojeh M. Prevalence of sepsis among Iranian newborns with jaundice: A meta-analysis based on cross-sectional studies. World J Peri Neonatol 2022; 4(2): 115-23.
2. Haile MT, Girma H. Prevalence and contributing factors of neonatal jaundice in neonatal intensive care unit at St Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, 2019. J Heal Med Nurs 2020; 74: 21-6.
3. Fakhri M, Farhadi R, Mousavinasab SN, Yosefi SS, Hosseinimehr J, Azadbakht M. Effect of natural products on jaundice in Iranian neonates. Jundishapur J Nat Pharm

Prod 2019; 14(1): e83042.
4. Lookzadeh MH, Mirjalili SR, Ekraminasab S. Immune and non-immune etiology of thrombocytopenia: Neonatal and maternal causes. World J Peri Neonatol 2021; 3(2): 78-86.
5. 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.
6. Manouchehrian M, Shakiba M, Shariat M, Kamalinejad M, Pasalar M, Jafarian AA, et al. Efficacy of maternal chicory aroma water consumption for neonatal jaundice: A randomized single-blind clinical trial. GMJ 2017; 6(4): 312-8.
7. Raghuvanshi D, Dhalaria R, Sharma A, Kumar D, Kumar H, Valis M, et al. Ethnomedicinal plants traditionally used for the treatment of jaundice (Icterus) in himachal pradesh in western Himalaya-A review. Plants (Basel) 2021; 10(2): 232.
8. Raeisi R, Heidari-Soureshjani S, Asadi-Samani M, Luther T. A systematic review of phytotherapies for newborn jaundice in Iran. Int J Pharm Sci Res 2017; 8(5): 1953-8.
9. Khoshdel A, Kheiri s. Effect of shir-e-khesht (billinaster drop) consumption by the neonates or their mothers on the neonatal icter [in Persian]. J Shahrekord Univ Med Sci 2011; 13(4): 67-73.
10. Ebrahimi S, Ashkani-Esfahani S, Poormahmudi A. Investigating the efficacy of Zizyphus Jujuba on neonatal jaundice. Iran J Pediatr 2011; 21(3): 320-4.
11. 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.
12. Ameli Z, Assarroudi A, Akrami R. Effect of bilineaster drop on neonatal hyperbilirubinemia. Evid Based Care 2017; 6(4): 66-73.
13. Rafieian-Kopaei M, Khoshdel A, Kheiri S, Shemian R. Cotoneaster: A safe and easy way to reduce neonatal jaundice. J Clin Diagnostic Res 2016; 10(4): SC01-3.
14. Monsef A, Eghbalian F, Rahimi N. Osong public health and research perspectives comparison of purgative manna drop and phototherapy with phototherapy treatment of neonatal jaundice :A randomized double-blind clinical trial. Osong Public Heal Res Perspect 2019; 10(3): 152-7.
15. Rezapour M, Mozaffarpur SA, Nikpour M, Alijanpour M. The effect of herbal medicine on neonatal jaundice : a systematic review. Int J Pediatr 10(2): 15377-88.
16. Basati G, Anbari K, Abbaszadeh S, Hamidi M. Medicinal plants used for neonatal jaundice in Shahrekord: An ethnobotanical study. J Med Plants By-products 2019; 2: 201-6.
17. Fakhri M, Farhadi R, Azadbakht M, Akbari J, Yousefi SS, Mousavinasab N, et al. Cotoneaster manna oral drop for the management of neonatal hyperbilirubinemia; a randomized, double-blinded and placebo controlled clinical trial. Immunopathol Persa 2022; 8(1): 1-8.
18. 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. J Ethnopharmacol 2019; 23(236): 240-9.
19. Fallah R, Fallahzadeh M, Noori-Shadkam M. Evaluation of safety and efficacy of purgative manna (Billinaster Drop) and glycerin suppository in icterus of healthy term newborns. Curr Drug Saf 2014; 9(1): 29-33.
20. Kicel A. An overview of the genus cotoneaster (Rosaceae): Phytochemistry, biological activity, and toxicology. Antioxidants (Basel) 2020; 9(10): 1002.
21. Panahandeh G, Khoshdel A, Sedehi M, Aliakbari A. Phytotherapy with hordeum vulgare: A randomized controlled trial on infants with jaundice. J Clin Diagnostic Res 2017; 11(3): SC16-9.
22. Sajedi F, Fatollahierad S. Effect of purgative manna on neonatal hyperbilirubinemia: A systematic review and meta-analysis. Iran J Pharm Res 2019; 18(2): 1020-31.
23. Azadbakht M, Pishva N, Samani SM, Alinejad F. The effect of purgative manna on the infant jaundice. Iran J Pharm Sci 2005; 1(2): 95-100.
24. Huang W, Zhang J, Moore DD. A traditional herbal medicine enhances bilirubin clearance by activating the nuclear receptor CAR. J Clin Invest 2004; 113(1): 137-43.
25. Lookzadeh MH, Bahrami R, Ekraminasab S. Prevalence of urinary tract infection in Iranian newborns with jaundice: A meta-analysis.

World J Peri Neonatol 2021; 4(1): 40-9.
26. Amiri MS, Joharchi MR, TaghavizadehYazdi ME. Ethno-medicinal plants used to cure jaundice by traditional healers of Mashhad, Iran. Iran J Pharm Res 2014; 13(1): 157-62.
27. Salehi A, Ostovar M, Marzban M. A systematic review and meta-analysis on the effect of Cotoneaster manna on neonatal jaundice. J Med Herb 2018; 9(1): 47-54.
28. 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.
29. 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.