Review Paper

The Effect of Chicory on Bilirubin Level in Newborns Suffering From Jaundice: A Systematic Review

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ABSTRACT

Background: Jaundice is the most prevalent reason for infants' hospitalization during their first month of birth, and herbal medicine has long been used alongside phototherapy to treat this problem.

Objectives: The present systematic review investigates chicory's influence on bilirubin levels in infants with jaundice.

Methods: In this systematic review study, Iranian databases, including Barekat Gostar, Scientific Information Database (SID), Irandoc, and Magiran, along with international databases, including Cochrane Library, Web of Science, Scopus, PubMed, and Google Scholar search engines were explored with relevant keywords to retrieve pertinent studies.

Results: Among the 7 selected articles with a sample size of 408 (204 people in the intervention group and 204 in the control group) from 2006 to 2020, 4 studies were in vitro and 3 were randomized clinical trials. Among these studies, mothers' pregnancy duration ranged between 30.9 and 38.8 weeks, infants' age ranged between 3 and 7 days, and their weight ranged between 1544 and 3316 g. Although chicory administration varied across the studies, 4 studies reported its effectiveness in reducing infants' bilirubin, whereas the other 3 articles reported no effect of chicory on bilirubin levels in infants.

Conclusions: Iran was the only country that evaluated the effect of chicory on neonatal jaundice in the form of several research studies. However, due to the limited number of studies and the different dosages of chicory, the way of consuming chicory, the type of studies, and the age and weight of babies, we could not reach a general conclusion on the efficacy of chicory.

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Introduction

Jaundice is a prevalent complication from which 60% of term newborns and 80% of premature newborns suffer over the first week of their lives [1, 2]. The largest number of severe neonatal hyperbilirubinemia incidences has been reported in Asia. Neonatal hyperbilirubinemia incidence has been reported to cause one-third of infant hospital admissions in Iran [3].

Although phototherapy is the primary treatment for hyperbilirubinemia, it exposes newborns to serious complications such as dehydration, retinal damage, diarrhea, and bronze-baby syndrome [4]. Hence, traditional drugs—especially herbal medicine—are used to reduce blood exchange frequency and phototherapy duration or as an alternative for these treatments [5]. Fumitory, jujube, chicory, mana, and cotoneaster have also been mentioned in our culture as treatments for this complication. These plants reduce bilirubin levels due to their laxative effects, increasing bowel movement frequency and intestinal bilirubin excretion [6].

Chicory (*Chicorium intybus*) is a perennial herbaceous plant from the *Asteraceae* family. It is among the most common plants in the Iranian diet in concentrate, infusion, etc. This plant is rich in inulin, a member of the fructan family, and a good water-soluble agent. Human digestive enzymes barely hydrolyze it, and thus it has many health benefits for cardiovascular and gastrointestinal problems [7-9]. Chicory is a 30- to 120-cm-high perennial plant from the composite family with reported anti-oxidant, anti-diabetic, anti-allergic, laxative, anti-inflammatory, diuretic, and anti-jaundice properties [10, 11]. Given its cold temperament, chicory is reported to have several medicinal benefits, such as protection against jaundice, reduced bile concentration, and improved liver function [12, 13].

Thanks to its flavonoid content, including quercetin, apigenin, and luteolin, which stimulate the UDP-glucuronosyltransferase enzyme, chicory accelerates bilirubin excretion [14]. The aforementioned is important in newborns given their premature liver function, UDP-glucuronosyltransferase deficiency at birth, and hepatic intestinal blood circulation due to high β-glucuronidase in the intestines concentration in full term and preterm infants. These are newborns' main causes of icterus [1, 15, 16]. However, given the contradictory results of previous studies on the effect of chicory on bilirubin levels in newborns [5, 14, 17-20], the present study seeks to examine the influence of chicory on bilirubin levels in newborns who have jaundice through a systematic review. It must be noted that the present study is the first to perform a systematic review in this field.

Methods

Study design

The present study is a systematic review examining the influence of chicory on bilirubin levels in newborns with jaundice. The study has been compiled based on the PRISMA (preferred reporting items for systematic reviews and meta-analyses) checklist [21].

Research population

The research population in the present study included all newborns who have jaundice.

Outcome

The primary outcome of the present study was determining the influence of chicory on bilirubin levels in newborns with jaundice.

Search strategy

Two authors carried out the reference search process. Iranian databases, including Baerkat Gostar, Scientific Information Database (SID), Irandoc, and Magiran, as well as international databases, including Cochrane, Web of Science, Scopus, PubMed, and Google Scholar search engines, were explored without language and time limitation using relevant MesH terms of "bilirubin", "chicory", "infant", "jaundice", and "systematic review" and their Persian equivalents to retrieve pertinent studies (updated as of April 2022). Combinations of the keywords were also searched on the mentioned databases using "AND" and "OR" operators. The initially retrieved studies were entered into EndNote 7 at this stage to detect duplicate studies quickly by referring to the software, and only one study was kept from each group of duplicate studies. The list of the references mentioned in all initial studies remaining by the end of the PRISMA flowchart was then used for a manual search. Table 1 contains an example of the search strategy in some databases.

PICO components

PICO comprised population (infants with jaundice), intervention (chicory), comparison (a group of infants used sterile water instead of chicory and underwent phototherapy), and outcome (bilirubin level in infants who have jaundice).

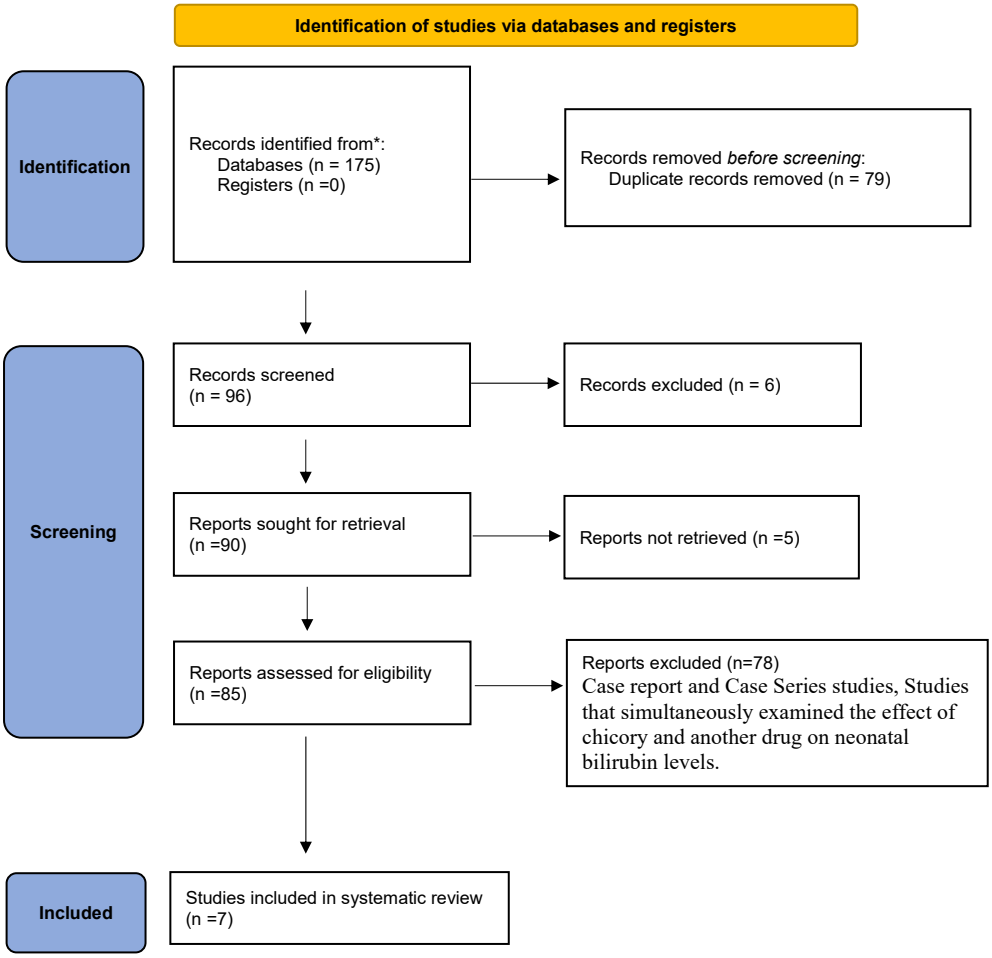

Figure 1. The flowchart of studies included in the systematic review process

Inclusion criteria

We entered into this systematic review in vitro and randomized controlled trials examining the influence of chicory on bilirubin levels in infants with jaundice. The intervention group received chicory, while the control or comparison group included infants undergoing phototherapy. Chicory was administered in the intervention group orally, through bathing with chicory extract, and by adding chicory extract to infants' blood samples under laboratory conditions.

Exclusion criteria

The exclusion criteria were Low-quality studies based on the quality assessment checklist, case studies or case report studies, full-text unavailability, and studies investigating the influence of chicory and other drugs on bilirubin levels in infants simultaneously.

Qualitative assessment

To assess the quality of RCT studies, two researchers used the Cochrane collaboration's checklist to evaluate the risk of bias in randomized trials, including 7 items, each examining one important dimension or type of bias in clinical trials. Each item on the checklist had 3 options "low risk", "high risk", or "unclear risk" [22] . JBI (The Joanna Briggs Institute) checklist for assessing the quality of experimental studies was also used to assess the quality of in vitro studies. The checklist included 9 questions, each with the 4 options of yes, no, unclear, and non-applicable, where "yes" gets one score and "no", "unclear", and "non-applicable" get zero scores [23]. After the risk of bias was assessed in all studies, the inconsistencies between the options of items were examined in each study, and all inconsistencies were resolved by reaching an agreement between the two assessors (Appendix 1, 2).

Table 1. Data collected from studied articles

Author, Year of publication (R)	Term or Premature Infants	Type of Study	Place, City	Number of Infants (Boys-Girls)	Mean Pregnancy Age (wk)	Mean Infant Age (d)	Mean Weight at Birth (g)	Chicory Administration	Chicory Dose and Execution Method	Qualitative assessment	Results
Badiehneshin et al. 2022 [5]	Full term	RCT	Rafsenjan	200	38.83	-	3316	Oral	Mothers consumed 70cc chicory thrice daily from week 36 until the second week of breastfeeding.	High quality	Jaundice was less prevalent in the intervention group than in the control group, but the difference was not significant (chi-square test, P=0.11). Bilirubin level was not significantly different between the two groups on the 1st days after birth. Still, this difference became significant on the third day, so the intervention group had lower bilirubin levels (independent t-test, P<0.05). Results suggested that mothers' chicory consumption could reduce bilirubin levels in infants.
Shariati, 2018 [20]	Preterm	In vitro	Birjand	21 (11-10)	30.9	-	1542	Sampling infants' blood	Half of the obtained serum volume after division	6	Mean total serum bilirubin was 5.62±2.3 and 0.19±0.07 mg/dL before and after the intervention in the case group, respectively (P<0.001). The average changes in total bilirubin were 5.15±1.70 and 5.43±1.99 mg/dL in the distilled water and chicory groups, respectively (P=0.62). Bilirubin changes after intervention were significantly smaller in the chicory group than in the control group. (0.32±0.11 mg/dL vs. 0.15±0.13 mg/dL, P<0.001). Results indicated that distilled water and chicory sweat reduced total and indirect serum bilirubin levels. Indirect bilirubin changes were not significant in either of the two groups, and total bilirubin changes were not significantly different between the two groups. Overall, results indicated that consuming chicory did not reduce bilirubin levels significantly.
Mohammadi Pirkashani et al. 2017 [14]	Full term	RCT	Isfahan	64 (34-30)	37.19	5.37	2960	Bathing in the extract	Infants were bathed in 500 mg chicory extract for 5-7min.	High quality	Results suggested that bilirubin serum levels did not vary significantly between the two groups upon hospitalization (P=0.37), whereas infants in the phototherapy group had a significantly higher bilirubin level than infants undergoing both phototherapy and chicory extract baths 24 (P=0.014) and 48 (0.011) hours after the intervention. The average changes in the bilirubin level of infants over the 48 hours after the intervention was -5.67±3.08 mg/dL in the phototherapy group and -9.30±3.22 mg/dL in the phototherapy and chicory extract bath group. Thus, a chicory extract bath alongside phototherapy can effectively reduce infant jaundice.

Author, Year of publication (R)	Term or Premature Infants	Type of Study	Place, City	Number of Infants (Boys-Girls)	Mean Pregnancy Age (wk)	Mean Infant Age (d)	Mean Weight at Birth (g)	Chicory Administration	Chicory Dose and Execution Method	Qualitative assessment	Results
Manoucehrian et al. 2017 [17]	Full term	RCT	Tehran	72 (36-36)	-	-	3397	Oral	200 mL twice daily, morning and evening, for 40 days before giving birth. Both groups were in their third trimester.	High quality	The results of this study demonstrated no statistically significant difference in terms of mean bilirubin levels between women consuming chicory-infused water and the control group. Moreover, consuming chicory-infused water was not significantly associated with a reduced need for phototherapy (P>0.05). Results suggested that taking chicory-infused water in pregnant women could not improve jaundice in infants.
Nabavizadeh et al. 2009 [18]	Full term	In vitro	Yasouj	-	-	3-7	Over 2500	Blood sampling	50 µg/mL	7	Among all herbal extracts, only chicory reduced indirect serum bilirubin. Although chicory resulted in lower levels than the control group, the difference was not statistically significant. Results indicated that chicory extracts directly affected bilirubin, so further research is required to distinguish the effective agents in chicory.
Nasirian et al. 2008 [19]	Full term and preterm	In vitro	Mashhad	30 (23-7)	-	7.35	2961	Sampling infants' blood	Hydroalcoholic chicory extract (100 lambdas) (50 g chicory was added to 250 cc alcohol and 50cc water at a 6% concentration)	6	The mean difference observed in conjugated bilirubin levels was 2.38±3.84 mg/dL in distilled water samples and 0.32±0.29 mg/dL in chicory samples. This study found that chicory does not significantly affect the level of bilirubin reported by the laboratory in vitro.
Nabavizadeh et al. 2006 [24]	Full term	In vitro	Shiraz	21	--	-	-	Sampling infants' blood	A 20-mL blood sample was drawn from infants with hyperbilirubinemia at the beginning of blood exchange. 0.5 mL of the extract of five plants, including fumitory, chicory, Cotoneaster, jujube, and mangrove, prepared through hydro-alcoholic distillation was added to 1 mL of the serum of infants with hyperbilirubinemia.	8	Although all studied drugs can probably lower bilirubin in different ways, such as laxative effects, liver stimulation, and binding to bilirubin in the intestine, only chicory plant extract was revealed to be effective in vitro and without the influence of internal factors, and can thus play a part in lowering bilirubin.

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Data extraction

Two researchers extracted data from the studies separately to minimize the risk of bias in reports and errors in data collection. Researchers entered the data into a checklist including the name of the researcher, type of study, study title, execution year, execution location, mean of the infant age, mean of the infant weight, sample size, number of girls and boys, chicory administration type, and general study output. The third researcher examined the extracted data to resolve inconsistencies.

Data analysis

Since the study was a systematic review, qualitative data analysis was performed, and the results were reported qualitatively.

Results

Study selection process

A total of 175 articles were initially retrieved by searching the databases mentioned before. The titles of the articles were examined, and 79 duplicate studies were eliminated. The abstracts of the remaining 96 studies were examined, and 6 studies were excluded since their full texts were unavailable. Out of the remaining 90 articles, 83 were excluded due to the exclusion criteria, and 7 studies ultimately entered the quality assessment stage, all of which were of acceptable quality and entered the systematic review process (Figure 1).

Infants profile

Among the 7 studied articles with a sample size of 408 (204 infants in the intervention group and 204 in the control group) from 2006 to 2020, 4 studies were in vitro and 3 RCTs. Among these studies, mothers' pregnancy duration ranged between 30.9 and 38.8 weeks, infants' age ranged between 3 and 7 days, and their weight ranged between 1544 and 3316 g. Four studies examined infants' blood samples in vitro and compared serum bilirubin levels before and after the intervention; two studies administered chicory sweat orally by mothers. They examined its impact on jaundice in infants, and one study used chicory extract to bathe the infants and investigated its effect through dermal absorption. All the reviewed studies were performed in Iran, although no filter was used regarding location when exploring studies (Table 1).

Discussion

The results of previous research on the influence of chicory on reducing bilirubin levels in infants are still uncertain. However, the contradictions between the effects of various studies examined in the present systematic review may have stemmed from their differences in terms of chicory administration and dose and the type of study. It should also be noted that factors such as infants' gender and their weight at birth also affect the results. However, the limited number of studies prevented us from classifying them and comparing those under similar conditions.

Several studies reported chicory effectiveness in reducing infant bilirubin levels. Nabavizadeh et al. (2009) examined the influence of common herbal drugs on reducing jaundice in infants using in vitro techniques. They reported that only chicory extract indirectly reduced serum bilirubin levels among all herbal extracts. Still, no significant difference was observed between the direct bilirubin levels of the two groups, although the chicory group had a lower bilirubin level than the control group [18]. Badiehneshin et al. (2022) examined the impact of chicory extract administration by mothers on the frequency of jaundice and serum bilirubin level in infants. They reported that the intervention group had a lower bilirubin level than the control group. Still, the difference was not significant (P=0.11). Moreover, the mean bilirubin level difference between the two groups was not significant on the first day of birth. Still, the intervention group had a significantly lower bilirubin level than the control group by the third day after birth (independent t-test, P<0.05). These results suggest that chicory administration by mothers can reduce bilirubin levels in infants effectively [5].

Mohammadi Pirkashani et al. (2017) conducted a randomized double-blinded clinical trial on 64 infants with jaundice in a selection of Isfahan hospitals. They examined the impact of bathing in chicory extract in these infants. Their results suggest that mean bilirubin levels were not significantly different between the two groups at admission (P=0.37). In contrast, the mean bilirubin level of infants in the phototherapy group was significantly higher than infants that underwent phototherapy and were bathed in chicory extract 24 h (P=0.014) and 48 h (P=0.011) after the intervention. Mean±SD bilirubin level variation in the infants in the 48-h phase after the intervention was -5.67±3.08 mg/dL in the phototherapy group and -9.30±3.22 mg/dL in the chicory extract bath group. Thus, bathing in chicory extract could reduce jaundice in infants [14]. Given its laxative effects, chicory reduced bilirubin levels in infants with jaundice by increasing their number of stools.

On the contrary, several studies reported chicory to be ineffective in reducing bilirubin levels. Shariati et al. (2018) conducted a study to examine the effects of phototherapy and chicory extract on serum bilirubin in premature infants hospitalized in a neonatal intensive care unit. Their results suggested that distilled water and chicory sweat reduced the total and indirect bilirubin levels. Indirect bilirubin variation was not significantly different between the two groups, and total bilirubin variation was the same in both groups. Overall, chicory extract did not significantly reduce bilirubin levels in premature infants [20]. Manouchehrian et al. (2017) aimed to examine whether 40 days of taking chicory extract was associated with fewer jaundice symptoms. The result indicated that consuming chicory extract by pregnant women did not improve their infants' jaundice [17]. The study of Nasirian et al. (2008) seeking to examine in vitro effects of chicory on bilirubin levels in 30 infants in a neonatal intensive care unit suffering from jaundice found the Mean±SD difference in conjugated bilirubin levels to be 2.38±3.84 mg/dL in samples with distilled water and 0.32±0.29 mg/dL in samples with chicory. This study found that chicory did not influence reported bilirubin levels in vitro [19]. It would appear that further clinical trials are required to make definitive conclusions in this regard.

Conclusion

Out of the 7 examined studies, 4 reported that chicory had a positive impact on reducing bilirubin levels and improving jaundice in infants, while the other 3 studies reported no statistically significant influence of chicory on reducing infants' bilirubin. According to the results of this study, Iran was the only country that had evaluated the effect of chicory on neonatal jaundice in the form of several research studies. Still, due to the limited number of studies and the different dosages of chicory, the way of consuming chicory, the type of studies, and the age and weight of babies, we could not make a general and accurate conclusion on the efficacy of chicory. Thus, the effectiveness of chicory in reducing jaundice in infants is still debatable, and future researchers are recommended to perform further studies in this regard.

Study limitations

Some articles' full texts were unavailable. Also, the articles published in this regard were exclusively conducted in Iran. No information was available from other countries, and no data on chicory's influence on infants' jaundice was measured in relation to variables such as weight at birth, infant gender, and infant age.

Ethical Considerations

Compliance with ethical guidelines

The study protocol was registered on The International Prospective Register of Systematic Reviews (PROSPERO) (Code: CRD42022328982).

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Authors contributions

Conceptualisation and study design: Moloud Fakhri, Roya Farhadi, Mahmood Moosazadeh, Amirsaeed Hosseini, and Mohammad Azadbakht; Data analysis: Roya Farhadi, Amirsaeed Hosseini, and Moloud Fakhri; Results interpretation: Mahmood Moosazadeh and Vahidreza Berneti; Review and editing: Amirsaeed Hosseini and Moloud Fakhri; Final approval: All authors.

Conflicts of interest

The authors declared no conflict of interest.

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Appendix

Appendix 1. JBI critical appraisal checklist for experimental studies

Reviewer..... **Date**.....

Author..... **Year**.....

Record Number.....

	Yes	No	Unclear	Notapplicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	☐	☐	☐	☐
2. Were the participants included in any comparisons similar?	☐	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	☐
4. Was there a control group?	☐	☐	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	☐	☐	☐
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☐	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Appendix 2. Cochrane checklist for randomized clinical trial studies

		Low Risk	High Risk	Unclear Risk
1	Random sequence generation (selection bias)			
2	Allocation concealment (selection bias)			
3	Blinding of participants and researchers (performance bias)			
4	Blinding of outcome assessment (detection bias)			
5	Incomplete outcome data (attrition bias)			
6	Selective reporting (reporting bias)			
7	Other bias			

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