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# Phytotherapy with Silymarin: A Clinical Trial on Infants with Jaundice

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ABSTRACT

**Objective:** In this study, we aim to investigate the effects of silymarin in terms of reducing bilirubinemia in infants with hypercholesterolemia and under phototherapy.

**Materials and Methods:** In this study, 180 infants were randomly assigned to three groups. The intervention was performed with silymarin in the case group. The case, positive, and negative control groups underwent phytotherapy, while the negative control group did not have any treatment; meanwhile, the case group was orally administered with 4 mg/kg silymarin once every 12 h as well. The tests consisted of alanine aminotransferase (SGPT), alanine transaminase (SGOT), albumin levels at baseline and completion of the intervention, and TSB at baseline and then after 24-h intervals up to the infants' discharge.

**Results:** As per our findings, a significant difference was noted in terms of the duration of hospital stay between the case and control groups ($p<0.001$) in favor of the case group. Although there was no significant difference in certain factors such as total albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin between the case and positive groups ($p>0.05$), a significant difference was observed between the case group and the positive control with the negative control group.

**Conclusion:** Administering silymarin on infants with hypercholesterolemia (bilirubin factor) and under phytotherapy can be effective alongside the main therapies, as a significant difference was observed between the case and positive control groups in terms of length of hospital stay (but not with the control group), which indicates the effect of silymarin on hyperbilirubinuria.

**Keywords:** Silymarin, phototherapy, icterus, infants, jaundice

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## INTRODUCTION

Jaundice has been considered as a common condition among newborns. In total, 60% of term babies and 80% of preterm babies acquire jaundice in the first week of life (1, 2). Indirect bilirubin level may exceed 20 mg/dl, which, in turn, increases the risk for neurologic system disorders and bilirubin bonding with basal nuclei and brainstem nuclei (1).

Irrespective of the reason, treatment for hyperbilirubinemia has been concentrated on the prevention of neurotoxicity due to indirect bilirubin as neurotoxicity, due to indirect bilirubin, cannot be treated (3, 4). Phototherapy is still the primary method used to keep total serum bilirubin (TSB) levels under pathogenic level (4). However, in case of failure, exchange transfusion would be the last choice (3), which, in turn, can cause several complications for newborns (5). Despite having several advantages and being considered significant worldwide, phototherapy may cause some short-term complications such as disturbance of thermal equilibrium, interference in maternal-infant emotional interaction, disturbance of infant circadian rhythm, electrolyte imbalance, dehydration, "bronze baby" syndrome (6), damage to the DNA (7), and decrease in the duration of exclusive breastfeeding (8). Therefore, it is necessary to search for new treatment methods. Currently, complementary medicine plays a significant role alongside modern medicine so that in addition to phototherapy, different herbal drugs are taken to treat jaundice in Iran (9).

Silymarin has been suggested as one of the safe drugs for bilirubinemia-related disorders in newborns (10). Silymarin is the seed extract of a medicinal plant called Silybum marianum from family Carduus marianum. Silibinin has been identified as the most active compound of silymarin, which is known as an antioxidant and hepatoprotective agent used to treat many liver diseases and hepatotoxicity (11–15). Silymarin is also considered to be an active medicinal plant in other diseases, including nephrotoxicity (16, 17).

Although a study demonstrated that silymarin could be effective in treating jaundice in full-term babies and could decrease phototherapy duration significantly, further clinical trials should be conducted to confirm this argument (9). Therefore, regarding the importance of reducing phototherapy duration and associated complications and

transfusion and finding more effective therapies with fewer side effects for the treatment of jaundice, this study was conducted to investigate the effects of silymarin in reducing phototherapy duration in infants with jaundice.

## MATERIALS and METHODS

### Design and Setting

For this double-blind clinical trial, 180 infants hospitalized for jaundice (with indirect hyperbilirubinemia) in Hajar Hospital, Shahrekord, southwest Iran, were selected according to convenience sampling, and they were randomly assigned to three groups of 60 infants each. Certain underlying diseases such as birth weight, gestational age, gender, and type of delivery, as confounder factors were matched as much as possible between the three groups.

The case group underwent phototherapy and were treated with silymarin drop, and positive control group only underwent phototherapy. Also, the third group did not have undergone any treatment.

The infants who needed to undergo phototherapy according to the National Institute for Health and Care Excellence (18) are as follows: healthy infants with conjugated hyperbilirubinemia and nonhemolytic jaundice, term and near-term (34 weeks) infants with jaundice at 1–14 days, and infants with negative Coombs test. Maternal use of phenobarbital, need for transfusion, conjugated hyperbilirubinemia, nonhemolytic jaundice, ABO or Rh incompatibility, lack of breastfeeding for any reason, and G6PD deficiency in the infant were considered the exclusion criteria.

### Intervention

After enrolling the infants into this study, certain underlying data such as age, gender, type of delivery, birth weight, blood group, and gestational age were recorded in a checklist. The findings of daily observations and laboratory tests of separate blood samples were recorded in the checklist as well. These tests consisted of alanine aminotransferase (SGPT), alanine transaminase (SGOT), albumin levels at baseline and completion of the intervention, and TSB at baseline and then after 24-h intervals up to the infants' discharge.

To prepare silymarin drop, 50 ml silymarin solution, containing 12 mg silymarin per 1 ml, was used. Four mg/kg silymarin was orally administered to the case group once every 12 h. Then, the laboratory tests were conducted on the infants. Phototherapy was conducted on and continued in both case and positive control groups until serum bilirubin reached the normal range. Meanwhile, after each 2 h of phototherapy, the infants were breastfed.

### Ethical Considerations

In light of previous studies, no complication has been reported due to the use of silymarin in patients and newborns (19–21); moreover, no complication was seen in the examined infants. The parents of the studied infants provided written informed consent for their children's participation in this study after they were given necessary explanations on type, history, and specifications of the drug. Besides that, the data of all patients were kept confidential at all steps of and after the study. The Ethics Committee of the Shahrekord University of Medical Sciences provided the ethical approval (no. 91.1391) for the protocol of this study.

**Table 1.** Demographic characteristics at enrollment into the study

| Variable | Mean in case group | Mean in control group | p |
|---|---|---|---|
| Gender (female) | %52 | %53 | 0.747 |
| Infants' age (day) | 3.33±0.82 | 3.33±0.87 | 0.829 |
| Infants' weight (g) | 2885±294.7 | 2935±312.2 | 0.369 |
| Gestational age (week) | 36.3±1.26 | 36.02±1.27 | 0.943 |

**Table 2.** Frequency distribution of the infants according to blood group at enrollment into the study

| RH | Blood group | p | Case group | | Control group | |
|---|---|---|---|---|---|---|
| | | | | n | % | n |
| Positive | A | 0.412 | Positive | 8 | 13.3 | 8 |
| | B | | | 11 | 11.7 | 7 |
| | AB | | | 4 | 10 | 6 |
| | 0 | | | 13 | 16.7 | 10 |
| Negative | A | 0.384 | Negative | 9 | 13.3 | 8 |
| | B | | 6.7 | 4 | 13.3 | 8 |
| | AB | | 5 | 3 | 3.3 | 2 |
| | 0 | | 13.3 | 8 | 18.3 | 11 |

### Statistical Analysis

After a sufficient number of infants were enrolled and the data were gathered, independent t-test and paired t-test were used to compare the three groups. The data were analyzed via SPSSv16.

## RESULTS

With regard to the frequency of descriptive data on certain variables such as the infants' gender, weight, and gestational age, the groups were matched such that there was no significant difference in these variables between the case and control groups ($p>0.05$) (Table 1).

Premature infants are more likely to have problems with blood type incompatibility, while term healthy and healthy infants are less likely to be affected. Since the age and weight of the neonates were the same in the control and case groups, the results of this study have a higher validity. Maternal and infant blood types can have negative effects on infant jaundice if they are incompatible. Most blood type incompatibilities occur when most mothers have blood type O, while the baby has blood type A or B. Hence, Table 2 presents the frequency distribution in the two groups of the study according to eight subgroups: positive and negative A, positive and negative B, positive and negative AB, and positive and negative O. The results indicated no significant difference in the blood groups and subgroups between case and control groups ($p>0.05$).

Table 3 shows the analysis of the data on bilirubin, albumin, ALT, and AST in the two groups of the study before and after the treatment.

**Table 3.** Liver laboratory indices before and after treatment

| Variable | Step of study | P-value between case and control groups | Case group Mean±SD | Positive control group Mean±SD | Negative control group Mean±SD |
|---|---|---|---|---|---|
| Bilirubin (mg/dL) | Before treatment | 0.654 | 16.99±1.7 | 16.79±1.74 | 21.63±2.74 |
| | After treatment | 0.601 | 8.35±0.6 | 8.4±0.57 | 9.5±0.76 |
| | P-value between before and after treatment | – | <0.001 | <0.001 | <0.001 |
| Albumin (mg/dL) | Before treatment | 0.896 | 3.4±0.60 | 3.4±0.65 | 3.7±0.75 |
| | After treatment | 0.826 | 3.5±0.64 | 3.5±0.60 | 3.8±0.63 |
| | P-value between before and after treatment | – | 0.19 | <0.001 | <0.001 |
| ALT (per 1 L serum) | Before treatment | 0.632 | 40.33±4.84 | 40.33±4.87 | 43.37±5.15 |
| | After treatment | 0.683 | 38.88±4.00 | 39.2±4.45 | 40.3±4.98 |
| | P-value between before and after treatment | – | <0.001 | <0.001 | <0.001 |
| AST (per 1 L serum) | Before treatment | 0.616 | 53.18±9. 22 | 52.33±9.30 | 59.67±9.30 |
| | After treatment | 0.061 | 46.25±8.33 | 49.11±8.30 | 53.13±8.90 |
| | – | | <0.001 | <0.001 | <0.001 |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

**Table 4.** Duration of hospital stay

| Variable | Mean in case group | Mean in positive control group | Mean in negative control group | p |
|---|---|---|---|---|
| Duration of hospital stay | 33.4±0.67 | 56.3±0.70 | 61.5±0.82 | <0.001 |

**Table 5.** Urination times during hospitalization

| Variable | Mean in case group | Mean in positive control group | Mean in negative control group | p |
|---|---|---|---|---|
| Urination times | 7.9 | 4.43 | 5.6 | <0.001 |

**Table 6.** Number of bowel movements before and after the intervention

| Variable | Mean in case group | Mean in positive control group | Mean in negative control group | p |
|---|---|---|---|---|
| Number of daily bowel movements before the intervention | 3.7±1.9 | 3.9±1.9 | 3.8±1.8 | <0.001 |
| Number of daily stools after the intervention | 5.3±1 | 4.5±1.6 | 4.9±1.7 | <0.001 |

Mean±standard deviation for bilirubin factor in the pre-treatment stage was 16.99±1.7 in the case group, whereas it was 16.79±1.74 in the control group ($p>0.05$). In fact, the effectiveness of silymarin with phototherapy is significant for before and after treatment due to its effect on urination and defecation.

Table 4 shows the analysis of the data as regards duration of hospital stay among the groups of this study.

The patient's discharge was based on the length of stay and hospitalization. As shown in Table 4 and the results of statistical analysis show, in the control group (Silymarin & phototherapy) in the duration of 33.4±0.67, in the positive control group (only phototherapy) was 56.3±0.70 and for negative control group (without treatment) was 61.5±0.82 in the period of 56.3±0.70 improved and the infant was discharged from the hospital, which were statistically significant differences ($p<0.001$).

In this study, the average number of urination times in different groups was measured. As shown in Table 5, the mean number of urination times was 4.43 times per day (t/d) in the positive control group, 5.6 times per day (t/d) in the negative control group, and 7.9 times per day (t/d) in the case group, which showed a significant difference between the control groups (positive and negative) and the case group.

The number of bowel movements before and after the intervention was assessed in different groups. The results are shown in Table 6. Statistical results showed a significant difference between control groups (positive and negative) and the case group.

## DISCUSSION

In this study, we aimed to investigate the effect of silymarin in terms of reducing bilirubinemia in babies with hyperbilirubinemia. Moreover, in both case and positive and negative control groups, liver enzyme (ALT and AST) levels were noted to decrease after treatment, but with no significant difference between the two groups. However, despite increased albumin after the treatment in both groups, the increase was deemed insignificant in the case group.

Moreover, a prospective cohort trial examining the effect of incorporating silymarin to phototherapy demonstrated that silymarin caused certain factors such as ALT and AST to reach normal levels, in addition to reducing hospital stay in the case group (22). Besides that, silymarin has allowed albumin to reach normal level, which is inconsistent with the findings of this current study. This inconsistency can be attributed to the difference in the methodology of the two studies or representative of the quicker decrease in bilirubin potentially being independent of serum albumin level. In our study, silymarin also reduced bilirubin, which is consistent with the mentioned study, whereas in previous studies, silymarin caused albumin to return to normal, which is inconsistent with the current findings in this study.

Another study has investigated S. marianum as an effective drug for the treatment of liver diseases and found that 3.75 mg/kg silymarin along with phototherapy could be effectively used for the treatment of unconjugated hyperbilirubinemia as it has been noted to lessen the duration of hospital stay and further regulate SGOT and SGPT (10). A study on this subject has reported the optimal effects of silymarin in term infants with hyperbilirubinemia (8).

Studies have demonstrated that silymarin is a hepatoprotective compound (23), and according to the findings of this present study, silymarin can lead to a significant decrease in the duration of hospital stay in infants with jaundice, which can be attributed to the properties of the active compounds found in S. marianum. Silymarin is a complex chemical compound of this plant consisting of three isomer flavonolignans, i.e., silibinin, silychristin, and silydianin (15), to which several pharmacological properties, including antioxidant, have been attributed (20). Of these three compounds, silibinin has better bioavailability, is less affected by liver damage, and induces antioxidant, antifibrotic, and liver metabolic function-regulatory effects (21).

The action mechanism of silymarin can be a protection against liver cell injury with free radical scavenging, stabilization of liver cell membranes, modulation of the immune responses, and stimulation of hepatocyte protein synthesis (24). Antioxidants are chemical compounds known to counteract free radicals and reduce oxidative stress and thus are able to prevent a wide variety of diseases. These medicinal effects are exerted by active ingredients, antioxidants, and phenolic and flavonoid substances of the plant (24). Therefore, silymarin, which is a potent antioxidant, might be beneficial in other conditions, too.

Besides that, this present study demonstrated that liver enzymes (ALT and AST) decreased significantly after the treatment in both groups, but the difference in the reduction was deemed not significant. El-Kamary study found that silymarin was not significantly effective on ALT, AST, and direct bilirubin (6). This finding presents that the mechanism of quicker decrease in bilirubin among newborns with jaundice under treatment with both phototherapy and silymarin is independent of the metabolism in the liver.

To treat jaundice in infants in China, Oriental artemisia (Artemisia argyi) and licorice (Glycyrrhiza glabra) are used (25, 26). Studies show that jujube and cashews, mangosteen, and milk thistle are among the plants that improve the excretion of urine and feces in infants with jaundice (27). In Iran, Cotoneaster horizontalis is also used in treating neonatal jaundice. The results of studies show that this plant has reduced bilirubin and effective days of hospitalization of infants (28).

Previous studies have examined the effect of silymarin on neonatal jaundice. In our study, the effect of silymarin on neonatal jaundice in Shahrekord was investigated, wherein we determined that silymarin increased bilirubin excretion and treated jaundice by increasing the number of bowel movements and urination (10, 29). Some medicinal plants have a laxative activity and thus increase the frequency of urination and defecation, with the mechanism of reducing intestinal-hepatic blood flow and finally increasing intestinal excretion of bilirubin (10). Silymarin may have a similar mechanism to excrete bilirubin in the urine and feces and improve neonatal jaundice. In our study, silymarin may have improved jaundice in infants by increasing their urination and defecation, too. Because silymarin may cause bilirubin excretion in urine and feces, it is recommended that the effect of silymarin on urinary and fecal bilirubin excretion be evaluated in clinical trials.

Silymarin is the main ingredient in sage plant (Silybum marianum). No serious side effects have been reported for silymarin. This supplement has been determined to be safe for most people although there may be some interactions and contraindications. Sage extract has been used for centuries to treat a number of ailments. Thistle milk or Silybum marianum extract (silymarin) is generally used by humans, and its side effects are tolerable and usually transient such as digestive disorders (10, 28, 29). Silymarin is a useful antioxidant, and due to its anti-inflammatory and antioxidant properties, it can improve hepatitis and liver cirrhosis and prevent the growth of cancer cells, cell death, gallstone formation, indigestion, and jaundice. Medicinal plants and their active ingredients can cure diseases and medical disorders with their antioxidant properties (10, 29, 30).

## CONCLUSION

The findings of this study demonstrated that silymarin administration alongside phototherapy can led to a decrease in TSB and decreased duration of hospital stay compared to phytotherapy alone among the infants hospitalized for hyperlipidemia. Therefore, this phytotherapy can be used as a supplementary therapy alongside main therapies. Lack of differentiation between direct and indirect bilirubin and study of silymarin effects on these two levels of bilirubin are some of the limitations of this present study. Further studies are recommended to isolate active compounds of S. marianum and comparatively investigate their properties on jaundice.

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**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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**Author Contributions:** Concept – MH, RC; Design – MH, RC; Supervision – MH, RC; Resource – MH, RC; Materials – MH, RC; Data Collection and/or Processing – MH, RC; Analysis and/or Interpretation – MH, RC; Literature Search – MH, RC; Writing – MH, RC; Critical Reviews – MH, RC.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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