



Evaluating the effect of chicory on serum ferritin levels in transfusion-dependent B-thalassemia patients: a randomized clinical trial

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Introduction: Several approved iron chelators exist, but they may cause significant adverse reactions in some patients. It is essential to explore complementary treatments that enhance compliance and minimize side effects.

Objectives: This study aims to evaluate the efficacy of chicory in reducing serum ferritin levels in transfusion-dependent β -thalassemia patients

Methods: A randomized, double-blind, placebo-controlled trial was conducted at Ali-Asghar Children's Hospital in Tehran, Iran. Participants included individuals with transfusion-dependent β -thalassemia and serum ferritin levels exceeding 1000 nanograms per milliliter (ng/mL). A total of 110 patients were randomly assigned to receive either chicory syrup or a placebo for 8 weeks. Primary and secondary outcomes were compared between the intervention and control groups.

Results: All 110 enrolled patients had their ferritin levels measured at baseline and 2 months after initiating either chicory extract or placebo. Mean ferritin levels decreased in both the treatment group (918.28 ± 151.42 ng/mL) and the placebo group (799.145 ± 145.07 ng/mL), with a statistically significant difference ($P = 0.04$). Additionally, alanine transaminase (ALT) levels showed a significant decline in the treatment group (8.12 ± 13.49 U/L) compared to the placebo group (2.8 ± 6.65 U/L) ($P = 0.019$).

Conclusion: Our findings suggest that chicory extract may effectively reduce ferritin levels in patients with β -thalassemia. However, further research with larger sample sizes is warranted to validate these results and strengthen the evidence for the therapeutic potential of chicory.

Keywords: alanine transaminase, chicory, ferritin, β -thalassemia

Introduction

Hemoglobinopathies are among the most prevalent monogenic disorders worldwide, with an estimated 1–5% of the global population carrying genetic mutations associated with thalassemia^[1,2]. β -thalassemia, characterized by reduced or absent synthesis of β -globin chains, is predominantly found in

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HIGHLIGHTS

- Several approved iron chelators exist for patients with thalassemia, but they may cause significant adverse reactions in some patients and sometimes are not enough to decrease the iron. Exploring complementary treatments that enhance compliance and minimize side effects is essential.
- According to this randomized, double-blind, placebo-controlled trial, we suggest that chicory extract may effectively reduce ferritin levels in patients with β -thalassemia. However, further research with larger sample sizes is warranted to validate these results and strengthen the evidence for the therapeutic potential of chicory.

regions such as the Mediterranean, the Middle East, and India. However, due to recent patterns of global migration, the incidence of β -thalassemia is increasing in diverse populations, underscoring the urgent need for comprehensive management strategies within healthcare systems^[3–6].

Thalassemia major and thalassemia intermedia represent two distinct clinical forms requiring medical intervention. Thalassemia major necessitates lifelong blood transfusions, typically initiated within the first few months of life, whereas thalassemia intermedia may require transfusions only during episodes of acute anemia or for select patients^[3–6]. Unfortunately, the regular blood transfusions essential for the management of these conditions lead to iron overload, which can precipitate a range of serious complications.

Serum ferritin estimation has become the standard clinical assay for detecting iron overload in β -thalassemia patients, as plasma ferritin levels correlate with total body iron stores in the absence of inflammation. Each unit of transfused red blood cells introduces approximately 250 mg of iron, while the body can only excrete about 1 mg of iron daily. Consequently, a thalassemia patient receiving 25 units of blood annually may accumulate approximately 5 grams of excess iron each year if not managed with effective chelation therapy^[7]. Furthermore, individuals with thalassemia demonstrate increased intestinal iron absorption^[8], and patients with more severe forms of the disease may experience iron deposition in the reticuloendothelial system as a consequence of repeated transfusions.

Excess iron is highly toxic to cellular structures and can lead to severe and irreversible organ damage, resulting in complications such as cardiomyopathy, cirrhosis, growth retardation, and various endocrine disorders. Thus, maintaining iron levels within safe limits and preventing the deposition of iron in vital organs through effective iron-chelation therapy is crucial. Approved iron chelators include deferasirox (DFX), deferiprone (DFP), and deferoxamine (DFO)^[9–14].

For patients requiring regular blood transfusions, effective iron removal is one of the most critical components of management. Deferoxamine is typically administered via subcutaneous or intravenous routes, while deferiprone and deferasirox are available as oral formulations. Achieving effective iron removal often necessitates years of consistent treatment adherence. It is essential to recognize that iron chelation therapy can impose a significant treatment burden and financial cost on patients^[15–17].

While DFX is effective, it is associated with common side effects, including gastrointestinal disturbances, skin rashes, and elevations in serum creatinine or liver transaminases. Clinical trials indicate that abdominal pain occurred in 4.8% of thalassemia patients in the EPIC trial, with nausea and diarrhea reported in 3.8% and 7.8% of patients, respectively. Furthermore, 3.6% of patients experienced an increase in creatinine levels greater than 33% from baseline^[18,19]. Standard iron chelation therapies mainly deferoxamine (DFO), deferasirox (DFX), and deferiprone (DFP) are crucial for managing transfusion related iron overload in conditions like thalassemia. However, their effectiveness is hindered by significant side effects, toxicity, high costs, and difficulties in patient adherence^[20]. But, DFO requires inconvenient infusions and carries risks of neurotoxicity and infections^[20,21]. DFX, taken orally, improves adherence but can cause gastrointestinal and renal issues and is expensive^[21]. DFP, also oral, poses a risk of agranulocytosis, necessitating regular blood monitoring^[22]. All three drugs have limitations, including adherence issues, potential toxicities, high costs, and the need for careful patient selection and monitoring^[22].

Given the potential side effects associated with numerous contemporary pharmacological treatments, there is an increasing interest in identifying alternative therapies that demonstrate improved tolerability and exhibit fewer adverse effects. *Cichorium intybus* Linn, commonly referred to as chicory, has garnered attention due to its widespread distribution and diverse health benefits^[23,24]. Chicory root, which contains a high amount of inulin, helps improve iron absorption in the intestines^[25]. The fermentation of inulin by gut bacteria boosts iron solubility, facilitating easier iron uptake by the body^[25,26]. Both animal and human research demonstrate that supplementing with chicory increases plasma iron levels and enhances iron absorption in the digestive tract^[26]. Also, By enhancing iron

absorption, chicory might indirectly affect hepcidin levels via feedback regulation, but this has not yet been confirmed^[26]. Clinical trials involving patients with thalassemia have shown that chicory supplementation significantly decreases serum ferritin levels, indicating a reduction in iron stores in the body. This effect is likely attributed to improved iron metabolism, as well as potentially enhanced iron utilization or excretion, rather than a direct inhibition of ferritin production^[26].

Chicory is recognized for its rich array of bioactive compounds, including flavonoids, saponins, and tannins^[27], as well as vitamins, essential amino acids, and carbohydrates^[28]. These attributes suggest that chicory may serve as a promising alternative therapy for numerous health conditions. However, further research is essential to fully elucidate its therapeutic potential and establish its safety and efficacy in clinical applications.

Chicory metabolites have demonstrated antioxidant, anticancer, anti-inflammatory, and anti-hepatotoxic properties^[29,30]. It is considered relatively safe, with tolerable doses reported up to 1000 mg/kg/day in various studies^[31]. Although potential adverse effects from chicory, such as contact dermatitis, skin irritation, hives, itching, nausea, headache, and abdominal pain, have been documented, they occur infrequently^[26]. Additionally, chicory has been associated with significant reductions in fasting serum glucose, hemoglobin A1c (HbA1c), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) levels^[32]. Notably, a recent study by Shahvazian *et al* indicated that chicory may aid in reducing iron overload, serum ferritin, and liver enzyme levels^[26]. We hypothesize that chicory reduces serum ferritin levels in individuals with transfusion-dependent β -thalassemia through mechanisms involving its inulin content and prebiotic effects, which may influence iron absorption and metabolism. Because chicory's inulin, a soluble fiber, ferments in the colon, promoting beneficial bacteria like *Bifidobacteria* and *Lactobacilli*^[26–33]. This process may increase short-chain fatty acid (SCFA) production, enhancing intestinal acidity and iron solubility, potentially affecting absorption^[26–33]. It may also boost colonic mucin production, which can bind excess iron, reducing its absorption or aiding its excretion^[26–33]. Therefore, this randomized, double-blind, placebo-controlled clinical trial aims to investigate the effectiveness of chicory in lowering serum ferritin levels in individuals with transfusion-dependent β -thalassemia.

Methods

Study design

This study was a randomized, double-blind, placebo-controlled clinical trial designed to evaluate the effect of chicory on serum ferritin levels in transfusion-dependent β -thalassemia patients. The trial was conducted at Ali-Asghar Hospital from December 2020 to July 2022 (IRCT code: Clinical Trial Registry; registration number: IRCT20200219046546N1). Throughout the study, all participants continued their regular chelation therapy. This study followed the CONSORT guidelines for transparent and comprehensive trial reporting (<https://www.consort-statement.org/>). Written informed consent was obtained from each patient, and the study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1398.489). The trial adhered to the principles outlined in the Declaration of Helsinki. The study comprised a single phase in which patients were

randomized in a 1:1 ratio to receive either placebo or chicory syrup. The complete trial protocol is available in the supplementary material. This study has been reported in line with the CONSORT criteria (Fig. 1).

Patients and eligibility criteria

Transfusion dependence was defined as receiving at least eight transfusions or 100 ml per kilogram of body weight of leukoreduced packed red blood cells (RBCs) annually, or requiring frequent transfusions to maintain hemoglobin levels above 70 g/L within the 2 years preceding enrollment. At Ali-Asghar Hospital, patients received packed RBC transfusions at a rate of 0.5 U per 10 kg when hemoglobin levels fell below 70 g/L. Inclusion criteria included: transfusion-dependent thalassemia (TDT) patients aged 14 years or older; Eastern Cooperative Oncology Group (ECOG) performance status of 0-3; an estimated life expectancy of at least three months; no bleeding tendency for 4 weeks or more; and absence of any abnormal hemolytic factors. Exclusion criteria included: use of medications that could influence hemoglobin levels within three months

prior to enrollment; deficiencies in vitamin B12 and folate; presence of significant cardiopulmonary, cerebrovascular, liver, kidney, or other severe diseases; breastfeeding or being of child-bearing age without the intention of using contraceptive measures; known allergy to the study drug; or participation in another clinical trial.

Randomization, masking and treatment

A block randomization method with a block size 2 was used to assign each participant to the intervention group. The rand() function in Excel was utilized to create a random sequence within each block. A unique four-digit random code was employed to conceal the randomization process. To ensure allocation concealment, the intervention type (A or B) was documented on paper and placed inside a sealed black box. The two treatments (chicory syrup and placebo) were assigned to boxes A and B, with only the principal investigator having knowledge of which drug was in each box. For each patient entering the study, a sealed box was randomly selected, the corresponding drug was administered to the participant, and a third party

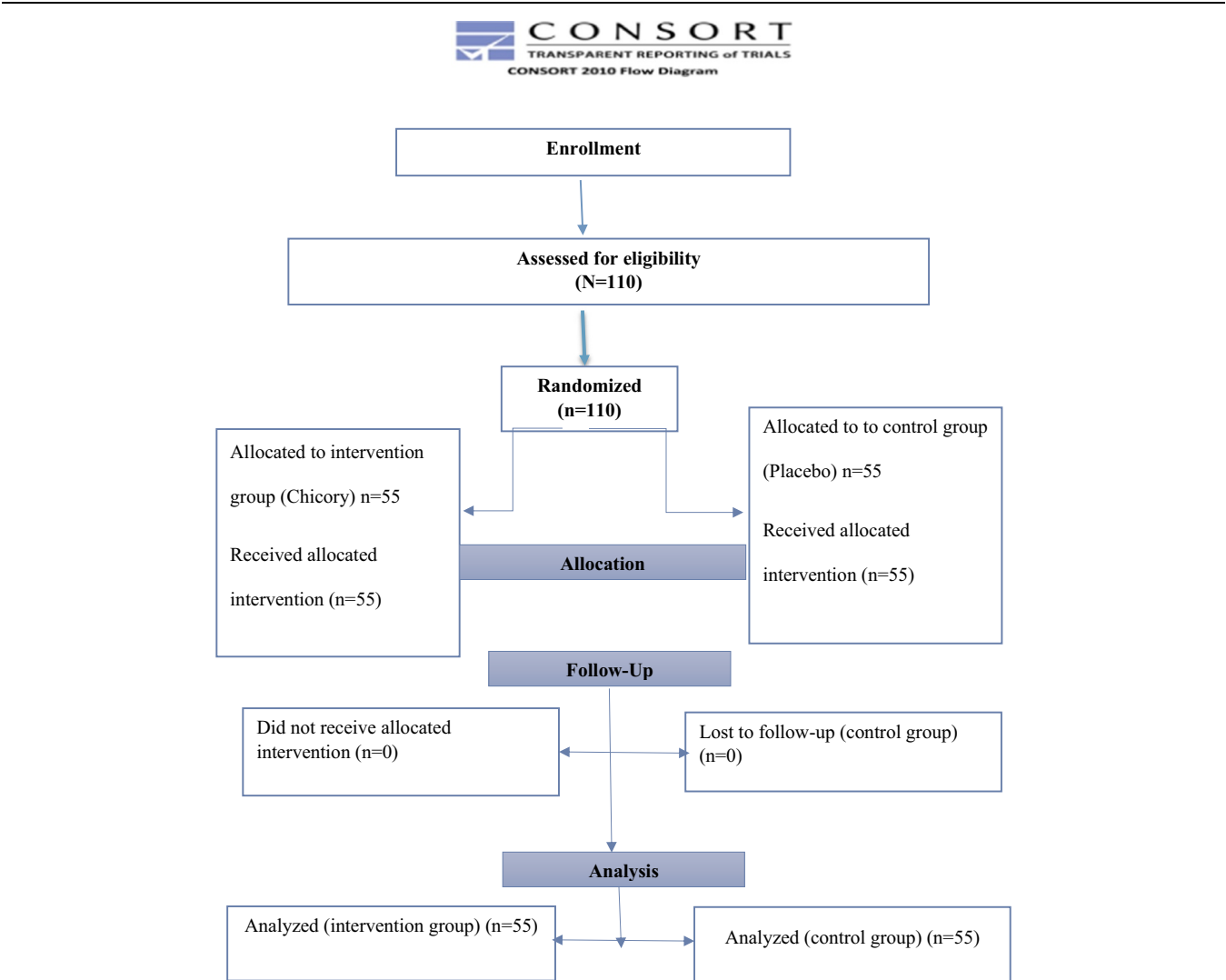


Figure 1. Flowchart of the progress through the phases of a randomized trial (i.e., enrollment, intervention allocation, follow-up, and data analysis).

recorded the assignment in the patient's case report form (CRF). The intervention group received 5 cc of chicory syrup twice daily for 8 weeks, while the control group received a placebo that matched the syrup in color, taste, and appearance. Previous studies examined time frames comparable to those in the current study to assess the impact of chicory syrup. In this study, the follow-up period was based on animal research, such as Eassawy *et al*'s 4-week study on the protective effects of chicory and/or artichoke leaf extracts against carbon tetrachloride and gamma-irradiation-induced chronic nephrotoxicity in rats^[34–36]. In this investigation, the duration was similarly set at 8 weeks. Chicory seeds and roots were sourced from the herbal medicine market and identified at the herbarium section of the Pharmacology Faculty of Tehran University, where they were assigned a herbarium code. Aquatic extracts from the seeds and roots were prepared using the maceration method and concentrated with a rotary evaporator. Each 5-cc dose of the extracted syrup contained 417 mg of both seed and root extracts. Prior to administration, the syrup was standardized for total phenolic and flavonoid content, and its concentration was adjusted to consist of 60% sugar by incorporating the concentrated chicory seed and root extracts. Patients were instructed to consume the syrup or placebo twice daily under medical supervision, and adherence to the regimen was monitored throughout the study period. The placebo syrup was formulated using the same basic components as the chicory syrup, resulting in a simple 60% sugar syrup. An approved edible brown food coloring was added to mimic the appearance of the chicory syrup. Both syrups were packaged in identical plastic containers.

Endpoints

The primary endpoint was the change in serum ferritin levels in patients treated with chicory syrup compared to those receiving placebo over the 8-week period. Serum ferritin levels were measured from blood samples collected at both baseline and the conclusion of the trial. Secondary endpoints included changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, as well as the incidence of adverse effects. Patient records were reviewed to gather demographic information, including age, gender, weight, genotype of thalassemia, and blood transfusion intervals.

Statistical analyses

Sample size determination was performed using Altman's nomogram. Data analysis was conducted using SPSS version 20.0. Primary and secondary outcomes were compared between the intervention and control groups utilizing Student's t-test at a two-sided, without correction for multiple comparisons. All statistical tests were two-sided, with *P* values less than 0.05 considered statistically significant.

Results

A total of 110 thalassemia patients (55 treatment, 55 placebo) with average age 26.7 years participated. Most had major thalassemia and half had transfusions every 3–4 weeks. After 2 months, the treatment group showed a significantly greater drop in ferritin (918 vs. 799 ng/ml; *P* = 0.04) and ALT levels (8.1 vs. 2.8 U/L; *P* = 0.019) than placebo (Fig. 2). Changes in AST were not significant

(Table 1). Changes in the levels of measured variables before, after, drug, and placebo administration are presented in Table 1.

Discussion

The present study demonstrates that chicory is effective in reducing serum ferritin levels in patients with β -thalassemia. These findings align with those of Shahvazian *et al*, who reported a reduction in serum ferritin levels following the use of chicory root. Similar to our results, they found no significant differences in the levels of AST and ALT^[26].

Zafar *et al* also observed changes in AST and ALT levels in their investigation, which highlighted the hepatoprotective effects of chicory against carbon tetrachloride (CCl₄)-induced hepatocellular damage. Zafar *et al* demonstrated that chicory extracts can protect the liver from damage caused by toxins like carbon tetrachloride. These extracts work by lowering elevated liver enzymes (AST, ALT, ALP) and bilirubin, restoring protein levels, and improving liver tissue structure. The protective effects were mainly linked to chicory's antioxidant activity and its ability to stabilize liver cell membranes, helping to prevent or reduce liver injury^[37]. Ahmed *et al* corroborated these findings, demonstrating the anti-hepatotoxic properties of chicory in albino rats subjected to CCl₄-induced liver damage, with histopathological analysis revealing nearly complete normalization of liver tissue without signs of fatty accumulation or necrosis. Also, Ahmed *et al* showed that chicory extract may effectively reduce ferritin levels and alanine transaminase (ALT) levels in transfusion-dependent β -thalassemia patients^[38].

Collectively, these studies underscore the potential anti-hepatotoxic effects of chicory. The mechanisms underlying these benefits are likely linked to its constituents, including isoflavones, polyphenols, and various antioxidants, which may mitigate the activity of serum ALT and AST during episodes of hepatotoxicity^[39].

Numerous investigations have established that chicory extract can significantly enhance liver function due to its antioxidant properties^[40–43]. Additionally, chicory has been shown to increase the activity of intracellular antioxidant enzymes, reduce oxidative stress, and bolster endogenous antioxidant defense systems in tissues^[44,45]. These attributes position chicory as a potent hepatoprotective agent, particularly advantageous for thalassemia patients who are especially susceptible to oxidative stress and hepatotoxicity stemming from elevated iron levels. Effective management of such patients necessitates pharmacological agents that can alleviate these hepatotoxic effects and prevent subsequent liver damage.

Beyond its hepatoprotective properties, chicory is also associated with a spectrum of other therapeutic benefits. Research has demonstrated its antibacterial, digestive, anti-inflammatory, diuretic, and anti-hypercholesteremic effects, all without any observed side effects^[44]. These diverse health benefits can be attributed to its rich array of active compounds, including inulin, sesquiterpene lactones, alkaloids, coumarins, flavonoids, unsaturated sterols, vitamins, saponins, and tannins, which possess significant medicinal value^[46,47]. Furthermore, studies suggest that dietary inulin may influence the regulation of genes encoding iron transporters in enterocytes, although the precise mechanisms by which it reduces serum ferritin levels are still not fully understood.

Limitations of the study

A limitation of this study was the short follow-up period of 8 weeks, which is insufficient for assessing the long-term effects

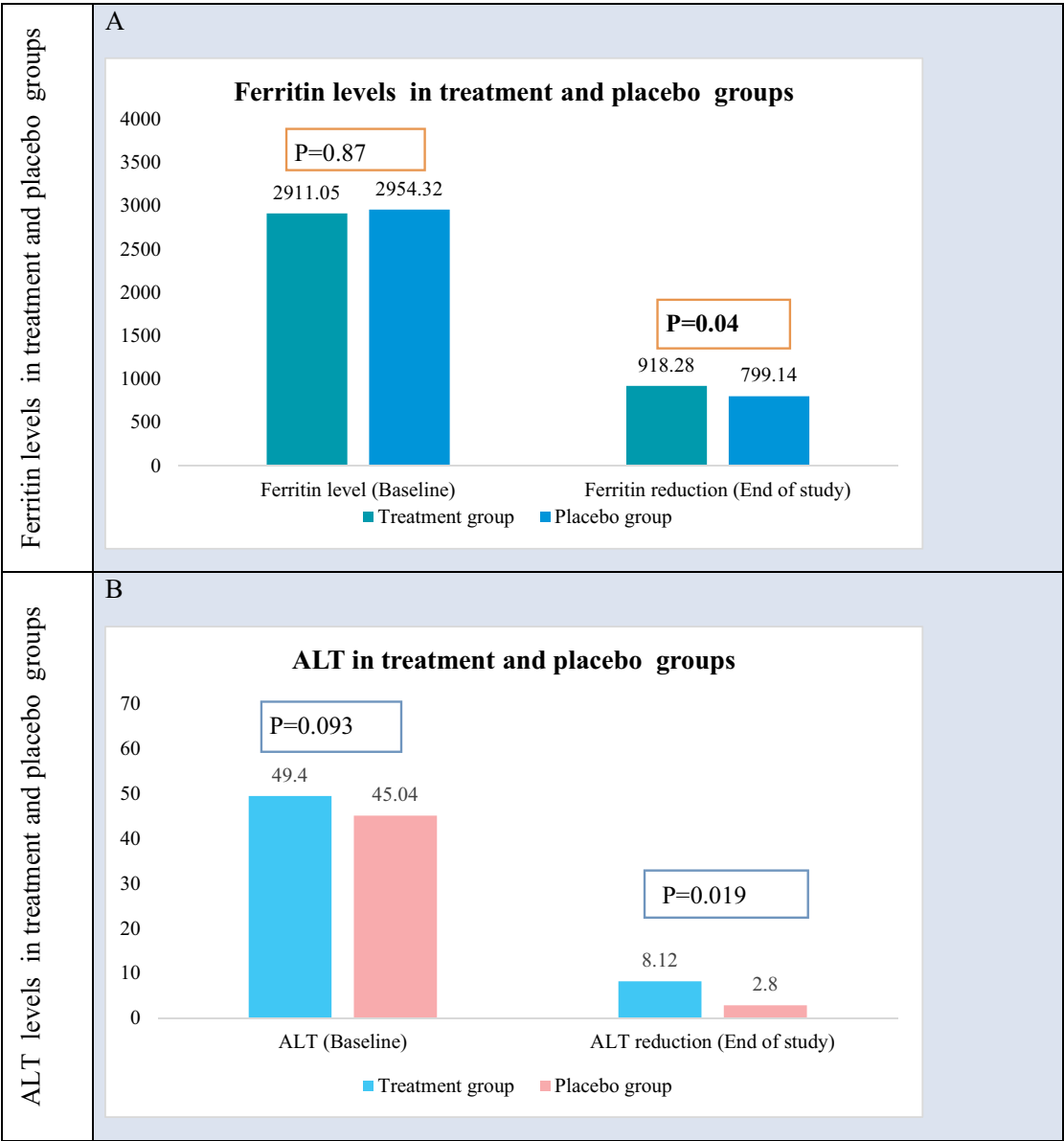


Figure 2. (A) Ferritin levels in treatment and placebo groups. (B) ALT levels in treatment and placebo groups.

of chicory on chronic iron overload. Another limitation of this study is its small sample size. Also, we did not address potential confounders such as dietary iron intake and chelation adherence. We recommend larger, longer-term trials with more rigorous control of external variables to confirm the efficacy and safety of chicory as a complementary treatment .

Table 1
Changes in the levels of measured variables before, after, drug, and placebo administration

Variables	Treatment group	Placebo group	P value
Ferritin level (baseline)	2911.05 (SD = 876.11) ng/ml	2954.32 (SD = 851.73) ng/ml	0.87
Ferritin reduction (end of study)	918.28 (SD = 151.42) ng/ml	799.145 (SD = 145.07) ng/ml	0.04 ^c
AST ^a (baseline)	53.92 ± 23.38 U/L	42.68 ± 19.92 U/L	0.79
AST changes (end of study)	10.88 ± 12.83 U/L (decrease)	11.28 ± 19.75 (increase)	0.39
ALT ^b (baseline)	49.4 ± 26.88 U/L	45.04 ± 40.10 U/L	0.93
ALT reduction (end of study)	8.12 ± 13.49 U/L	2.8 ± 6.65 U/L	0.019 ^c

^aAspartate transaminase.

^bAlanine transaminase.

^cSignificant.

Conclusion

The findings of this study indicate that the intake of chicory extract positively influences the reduction of ferritin levels in patients with thalassemia. To further validate these results, it is recommended that future research be conducted with larger sample sizes. Additionally, considering the absence of significant adverse effects associated with the use of chicory in both this study and previous research, it is advisable to consider this medicinal herb as a complementary treatment alongside existing chelating agents.

Ethical approval

Ethics Committee of Iran University of Medical Sciences reference number: IR.IUMS.FMD.REC.1398.489.

Consent

Written and signed consent has been obtained. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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None.

Author contributions

S.H.A.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software development, supervision, validation, visualization, writing – original draft, writing – review & editing; N.A.: formal analysis, methodology, writing – original draft, writing – review & editing; R.H.: methodology, writing – original draft, writing – review & editing; R.R.: data curation, software development, writing – review & editing; A.K.: investigation, software development, writing – review & editing.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

IRCT code: Clinical Trial Registry; registration number: IRCT20200219046546N1.

Guarantor

Neda Ashayeri.

Provenance and peer review

Our paper was not invited.

Data availability

The original datasets are available from the corresponding author upon reasonable request.

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