


Iron Status Improvement by Green Tea Supplementation in Transfusion-Dependent Thalassemia: Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Iron overload significantly contributes to organ dysfunction in transfusion-dependent thalassemia (TDT) patients. Green tea extract (GTE), rich in polyphenols with iron-chelating properties, has shown promise in reducing iron levels in these patients, although its effectiveness remains unclear. This study aims to evaluate the impact of GTE on iron status in TDT patients. **Methods:** A systematic search of the PubMed, Embase, and Cochrane Library databases was conducted up to July 2024, identifying randomized clinical trials (RCTs) based on predefined criteria. Iron status was assessed through serum ferritin, total iron binding capacity (TIBC), serum iron, and transferrin saturation. Five RCTs involving 217 participants were included. **Results:** There has been a significant reduction in serum ferritin in the GTE group compared to controls (mean difference MD -0.55, 95% CI: -0.81, -0.29) and a similar reduction in serum iron (MD -63.73, 95% CI: -106.46, -21.00). Significantly higher TIBC and lower transferrin saturation were also observed in the GTE group. **Conclusion:** These findings suggest that GTE supplementation lowers serum ferritin and serum iron in TDT patients. Further research with larger cohorts is needed to better understand the effects on diverse populations.

Keywords: Green tea, iron overload, serum ferritin, serum iron, thalassemia.

ABSTRAK

Pendahuluan: Penumpukan zat besi berlebih secara signifikan berkontribusi pada disfungsi organ pasien talasemia tergantung transfusi (*transfusion-dependent thalassemia*/TDT). Ekstrak teh hijau (*green tea extract*/GTE) kaya akan polifenol dengan sifat mengikat besi, berpotensi mengurangi kadar besi pasien-pasien ini, meskipun efektivitasnya masih belum jelas. Studi ini mengevaluasi dampak GTE terhadap status besi pasien TDT. **Metode:** Pencarian sistematis pada basis data PubMed, Embase, dan Cochrane Library dilakukan hingga Juli 2024, untuk mengidentifikasi uji klinis acak (*randomized clinical trial*/RCT) berdasarkan kriteria yang telah ditentukan. Status besi dinilai melalui feritin serum, kapasitas pengikatan besi total (*total iron binding capacity*/TIBC), besi serum, dan saturasi transferrin. Lima RCT yang melibatkan 217 peserta dimasukkan dalam studi ini. **Hasil:** Terdapat penurunan signifikan feritin serum pada kelompok GTE dibandingkan kelompok kontrol (perbedaan rata-rata MD -0.55, 95% CI: -0.81, -0.29) dan penurunan serupa besi serum (MD -63,73, 95% CI: -106,46, -21,00). TIBC lebih tinggi dan saturasi transferrin lebih rendah tidak signifikan juga diamati pada kelompok GTE. **Simpulan:** Temuan ini menunjukkan bahwa suplementasi GTE menurunkan kadar feritin serum dan besi serum pada pasien TDT. Penelitian lebih lanjut dengan kohort yang lebih besar diperlukan untuk lebih memahami efeknya pada populasi yang beragam. **William Prayogo Susanto, Cecy Rahma Karim. Perbaikan Status Zat Besi oleh Suplementasi Teh Hijau pada Talasemia Tergantung-Transfusi: Tinjauan Sistematik dan Meta-Analisis.**

Kata Kunci: Teh hijau, kelebihan zat besi, feritin serum, besi serum, talasemia.

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INTRODUCTION

Thalassemia is the most frequent inherited hemoglobinopathy, characterized by ineffective erythropoiesis and chronic anemia.[1] It is an autosomal recessive disorder, causing impairment of globin chain synthesis. The deficit in one type of chain is usually accompanied by another type of chain, resulting in an imbalance of globin chain types, promote the premature destruction of the erythrocyte.[2] Prevalence of thalassemia is relatively higher in South East Asia, Middle East Asia, South Asia, and the Mediterranean, with around 3%–10% of the population having a thalassemia gene trait.[3,4] The severity

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of thalassemia depends on the extent of the globin chain imbalance. The most severe type of thalassemia clinically is transfusion-dependent thalassemia (TDT), which requires regular red blood cell (RBC) transfusion.[3,4]

Routine RBC transfusion in TDT patients brings a considerable iron overload problem; each pack (300 mL) of RBC transfusion contains 250 mg iron, while our body doesn't have a natural effective way to excrete iron. Iron overload occurred after just 10 to 20 regimens of transfusion, leading to reactive oxygen species (ROS) generation, followed by lipid peroxidation. As iron is primarily stored in the liver, heart, and endocrine glands, the toxic effect manifested in these organs leads to heart dysfunction, liver fibrosis, hypothyroidism, and diabetes mellitus. To prevent these complications, iron chelator agents were included in the regimen. Deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX) are 3 iron chelators commonly used. The latter is the most popular, as it is administered orally and promotes the iron removal through fecal excretion.[5,6]

Green tea is known for its benefits due to its antioxidant and anti-inflammatory features.[7] Polyphenol compounds, such as tannin and tannic acid, are abundantly contained in the green tea leaves also have an iron chelator effect.[8] It reduces iron uptake in the intestine by forming a chelating complex, thus inhibiting the luminal absorption. This iron-chelating effect is also dose-dependent.[8] With the iron overload issue among TDT patients, green tea extract can be beneficial as an iron chelating agent. However, the iron chelating effect of polyphenols mainly occurs in the lumen absorption, while the iron source of TDT patients comes from the circulation. Several clinical trials have investigated the correlation of green tea extract with iron overload in TDT patients, but the conclusion still varies.

A systematic review and meta-analysis were conducted to determine the effect of green tea extract on iron status in TDT patients. We evaluated the serum ferritin, serum total iron binding capacity (TIBC), serum iron, and transferrin saturation to describe the iron status.

METHODS

Literature Search Strategy

Potentially relevant studies were searched in PubMed, Embase, and Cochrane Library without limitation of language, publication year, or study region. The following search terms are used: population (thalassemia or transfusion-dependent thalassemia), intervention (green tea extract), and outcome (serum ferritin or serum iron or total iron binding capacity or transferrin saturation). The search process was in accordance with PRISMA guideline,[9] up to July 2024.

Eligibility Criteria

The inclusion criteria: (1) intervention study, including randomized controlled trial and clinical trial, (2) transfusion-dependent thalassemia with routine therapy of iron chelator, and (3) iron status described by serum ferritin, serum TIBC, serum iron, or transferrin saturation.

The exclusion criteria: (1) literature types of review, meta-analysis, case report, and editorial article, (2) non-English literature, (3) minor thalassemia patient who didn't receive blood cell transfusion regimen routinely, and (4) comorbidities which affects the blood cell homeostasis.

Data Extraction

Study selection was performed in 2 steps: initial title and abstract screening, followed by complete text evaluation for its suitability for this study. The authors independently assessed the literature eligibility, followed by data extraction using data extraction sheets. Any discrepancies were addressed by consensus. The extracted data included: literature characteristics (title, author, publication year) and patients' characteristics (age, serum ferritin, serum TIBC, serum iron, transferrin saturation). Authors were contacted for the lack of relevant data.

Study Quality & Risk of Bias Evaluation

The modified Jadad scale and Cochrane's risk of bias tool were used to assess the study quality and bias risk of the eligible studies. The modified Jadad scale includes randomization process (2 points), blinding method (2 points), clear criteria description (1 point), study withdrawal or dropout (1 point), adverse effect assessment (1 point), and statistical analysis (1 point). Studies with 4–8 points were considered high quality, while 1–3 points showed a low-quality study.[10] The potential biases were evaluated using Cochrane's bias risk tool in accordance with the PRISMA statement.[11]

Statistical Analysis

Review Manager 5.4 software[12] was used to establish the forest plot. Continuous variables were measured by mean difference (MD) ± standard deviation (SD); 95% confidence interval (CI) was used for each variable. A heterogeneity test was done by a chi-square test. The fixed effect model was used if the homogeneity was low (I2< 50%); otherwise, the random effect model was used. If *p*-value < 0.05, the difference was considered statistically significant.

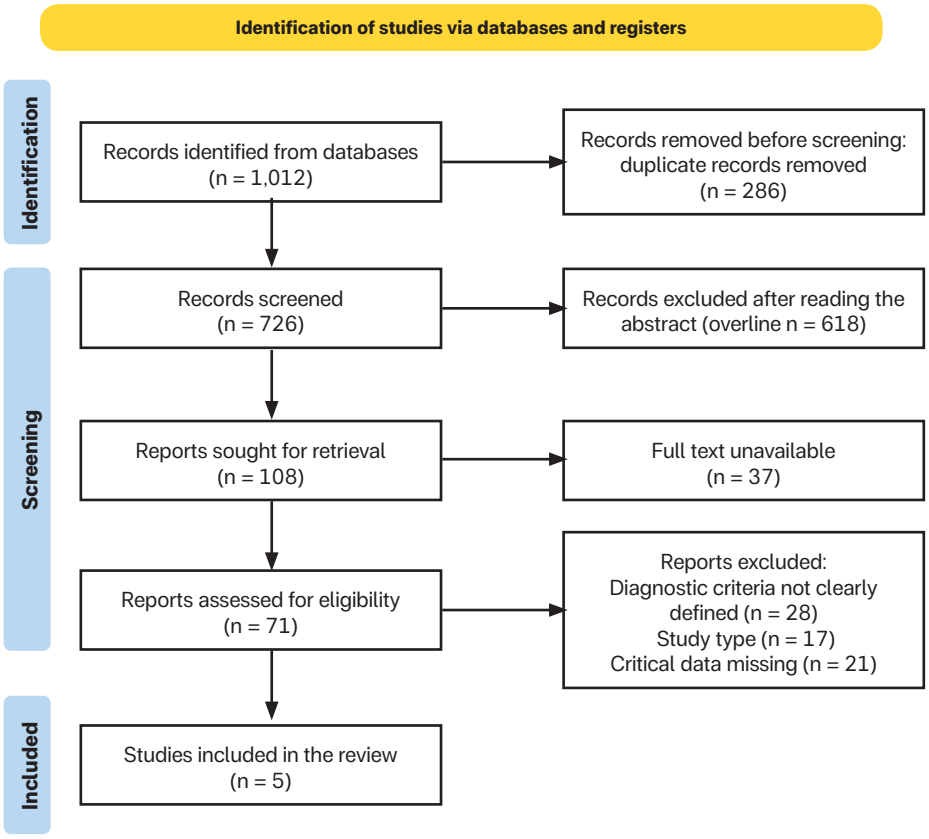
RESULTS

Search Results

The process of literature searches and screening is shown in **Scheme**. A total of 1,012 studies on green tea extract and iron status in transfusion-dependent thalassemia patients were retrieved from the databases. After screening by application of the inclusion and exclusion criteria, only 5 studies were included in the analysis.[13–17]

Characteristics of the Included Studies

All 5 studies included in this systematic review are randomized controlled trials (RCTs) with a total of 217 thalassemia patients. A summary of the included studies is presented in **Table 1**. All studies were conducted in Asia: 2 studies from Iran, 1 from Iraq, and 1 from Thailand. The age of participants varied widely; some studies focus on children and others on adults. Patients received regular blood transfusions, and most studies specified previous therapies such as iron chelation therapy, splenectomy, or low-dose aspirin therapy. The studies collectively investigated the effects of green tea interventions on thalassemia patients, utilizing various preparations and dosages. Patients were typically given green tea after meals, with doses ranging from 2 grams to 12 grams daily, across intervention periods spanning from 1 month to 12 months. Control group interventions varied from water regimens to usual treatments, while laboratory tests were conducted before and after the interventions to measure outcomes.



Scheme. PRISMA flowchart.

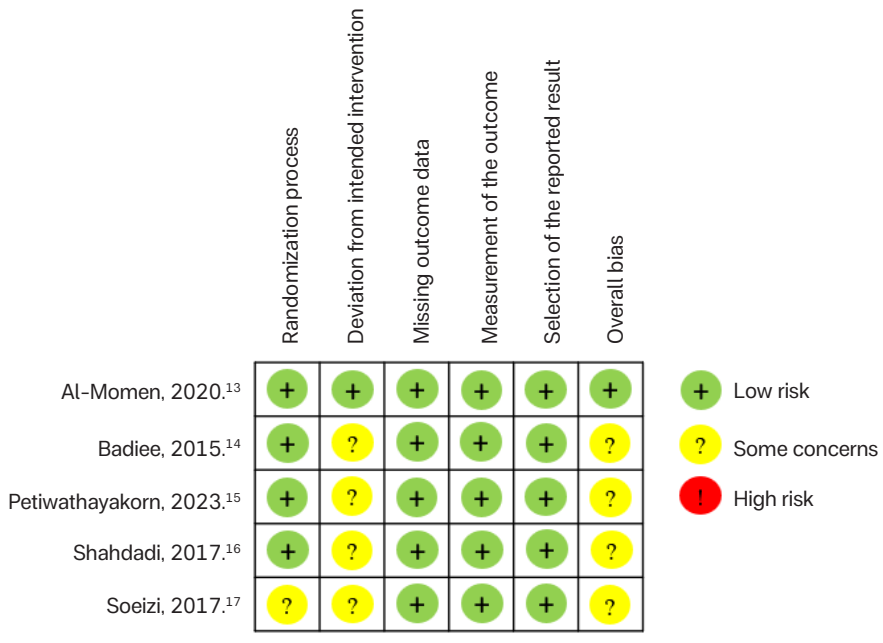


Figure 1. Risk of bias assessment.

The characteristics of the study populations are detailed in **Table 2**, and the intervention details are provided in **Table 3**.

Risk of Bias Analysis

The study by Al-Momen (2020)[13] exhibited an overall low risk of bias. Studies by Badiee (2015),[14] Petiwathayakorn (2023),[15] Shahdadi (2017),[16] and Soeizi (2017)[17] had some concerns overall, mainly due to deviations from intended interventions and, in the case of Soeizi, the randomization process **(Figure 1)**.

Overall, Al-Momen (2020)[13] stands out with low risk across all criteria. The rest of the studies exhibited some concerns, primarily in deviations from intended interventions. Their randomization processes, outcome measurements, and selection of reported results were consistently low risk across the studies; in Soeizi (2017)[17] the randomization process was not explained in detail, causing some concern on the assessment. When assessed using the modified Jadad score,[10] studies by Shahdadi (2017)[16] and Badiee (2015)[14] were considered low quality, as both assessments' scores were only 3 **(Table 1)**.

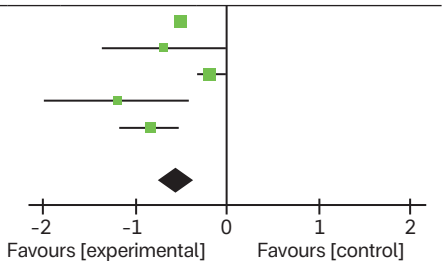
Effect of GTE on Iron Status

Significant differences in subjects receiving green tea extract were found in serum ferritin and serum iron level **(Figure 2).** Compared to the control, subjects with GTE supplementation showed a significantly lower serum ferritin with a mean difference (MD) of -0.55 mcg/dL (95% CI: -0.81, -0.29, $p < 0.0001$, I2 = 83%). Similar result was also shown in serum iron level, with MD of -63.73 mcg/dL (95% CI: -106.46, -21.0, $p = 0.003$, I2 = 91%). However, these results still show heterogeneity between studies. In serum TIBC (MD = 44.2, CI 95% -10.67, 99.08, $p = 0.11$, I2 = 76%), the GTE group showed a higher level, but it was considered statistically insignificant. The transferrin saturation (MD = -0.46, CI 95% -6.67, 5.74, $p = 0.88$, I2 = 0%) between the groups was quite similar, with no significant differences.

1.1 Serum Ferritin (mcg/dL)

Study or Subgroup	Year	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Al Momen[13]	2020	1.328	0.127	29	1.813	0.235	28	30.5%	-0.48 [-0.58, -0.39]
Badiee[14]	2015	2.5	0.766	14	3.183	1.05	14	10.0%	-0.68 [-1.36, -0.00]
Petiwathayakorn[15]	2023	0.622	0.185	19	0.815	0.185	11	29.3%	-0.19 [-0.33, -0.06]
Shahdadi[16]	2017	2.233	1.539	25	3.419	1.247	25	8.3%	-1.19 [-1.96, -0.41]
Soeizi[17]	2017	2.187	0.487	26	3.019	0.642	26	21.9%	-0.83 [-1.14, -0.52
Total (95% CI)				113			104	00.0%	-0.55 [-0.81, -0.29]

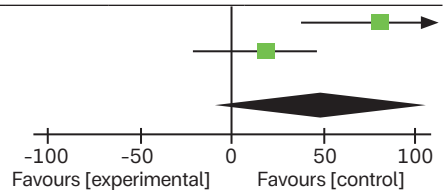
Heterogeneity: Tau² = 0.06; Chi² = 23.25, df = 4 (*p* = 0.0001); I² = 83%
Test for overall effect: Z = 4.17 (*p* < 0.0001)



1.2 Serum Total Iron Binding Capacity (mcg/dL)

Study or Subgroup	Year	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Badiee[14]	2015	311.6	58	14	239.1	46.4	14	49.5%	72.50 [33.59, 111.41]
Petiwathayakorn[15]	2023	301.7	46.9	19	285.2	51.9	11	50.5%	16.50 [-20.72,53.72]
Total (95% CI)				33			25	100.0%	44.20 [-10.27, 99.08]

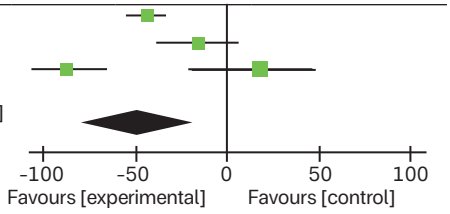
Heterogeneity: Tau² = 1190.64; Chi² = 4.16, df = 1 (*p* = 0.04); I² = 76%
Test for overall effect: Z = 1.58 (*p* = 0.11)



1.3 Serum Iron

Study or Subgroup	Year	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random,95% CI
Badiee[14]	2015	160	13.3	14	216.7	16.7	14	36.3%	-56.70 [-67.88, -45.52]
Petiwathayakorn[15]	2023	178.3	31.6	19	198.8	42.9	11	31.8%	-20.50 [-49.56, 8.56]
Soeizi[17]	2017	185.9	51.6	26	300.65	53.5	26	31.9%	-114.75 [-143.32, -86.18]
Total (95% CI)				59			51	100.0%	-63.73 [-106.46, -21.00]

Heterogeneity: Tau² = 1276.54; Chi² = 21.52, df = 2 (*p* < 0.0001); I² = 91%
Test for overall effect: Z = 2.92 (*p* = 0.003)



1.4 Transferrin Saturation (%)

Study or Subgroup	Year	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Petiwathayakorn[15]	2023	89.6	12.2	19	88.4	8.1	11	72.6%	1.20 [-6.08, 8.48]
Soeizi[17]	2017	88.58	23.9	26	93.45	19.51	26	27.4%	-4.87 [-16.73, 6.99]
Total (95% CI)				45			37	100.0%	-0.46 [-6.67, 5.74]

Heterogeneity: Chi² = 0.73, df = 1 (*p* = 0.39); I² = 0%
Test for overall effect: Z = 0.15 (*p* = 0.88)

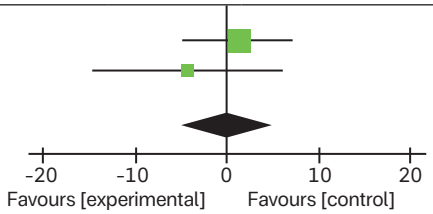


Figure 2. Comparison of iron status level between subjects receiving GTE extract and control.

Table 1. Summary of included study.

First Author	Year	Study Design	Country	Objective	Results	Modified Jadad Score
Soeizi[17]	2017	RCT	Iran	Examine the effects of green tea on serum iron parameters and antioxidant status in β-thalassemia major patients	Green tea significantly decreased serum iron, ferritin, and MDA levels, and increased TAC compared to the control group	8
Shahdadi[16]	2017	RCT	Iran	To determine the effect of green tea on iron overload in patients with major thalassemia	There was a significant difference between the mean serum ferritin in the two groups after green tea intervention.	3
Petiwathayakorn[15]	2023	RCT	Thailand	Assess the effects of GTE tablet consumption on coagulation, platelet function, and iron overload in TDT patients	GTE tablets significantly reduced platelet aggregation, increased plasma protein C and protein S activities, and decreased plasma ferritin levels in a time-dependent manner	8
Badiee[14]	2015	RCT	Iran	To explore the effects of GT against iron overload in β-thalassemia major patients who were under regular chelation therapy with DFO	Significant decrease in levels of iron, ferritin, LPO, and white blood cells, increase in TIBC levels after GT therapy	3
Al-Momen[13]	2020	RCT	Iraq	To understand the effects of green tea on iron balance in thalassemia intermedia patients	The net drop of liver iron concentration in the green tea group was significantly higher than the control group. Serum ferritin reduction in the green tea was significantly greater than in the control group. Hemoglobin levels were slightly higher in the green tea group compared with the control group, but this was not significant	7

Abbreviations: RCT: Randomized controlled trial; MDA = Malondialdehyde; TAC = Total antioxidant capacity; GTE = Green tea extract; TDT = Transfusion-dependent β-thalassemia; GT: Green tea; LPO = Lipid peroxidation; TIBC = Total iron binding capacity; DFO = Deferoxamine.

Table 2. Population characteristics.

First Author	Year	Study Population	Number of Population Experimental Groups	Age Means ± SD Experimental Group	Number of Population Control Groups	Age Means ± SD Control Group	Transfusion Acquired	Previous Therapy Acquired	Comorbidity
Soeizi[17]	2017	Patients with β-thalassemia major	26	23.1 ± 3.33	26	24.2 ± 3.15	One or two units of packed red blood cells every 3–4 weeks	Subcutaneous desferrioxamine as an iron chelator	None
Shahdadi[16]	2017	Patients with major thalassemia	25	14.34*	25	14.34*	Twice a month	Not specified	Not specified
Petiwathayakorn[15]	2023	transfusion-dependent β-thalassemia patients	19	32.6 ± 12.6	11	39.8 ± 10.1	Not specified	Iron chelation therapy, splenectomy, and low-dose aspirin therapy	Not specified
Badiee[14]	2015	Beta-thalassemia children	14	9–15#	14	9–15#	Not specified	Regular chelation therapy with deferoxamine (34 ± 4 mg/kg/day)	None
Al-Momen[13]	2020	Thalassemia patients	29	13.62 ± 4.27	28	13.47 ± 2.58	70.64 ± 7.84 mL/kg/year	Deferasirox iron chelation therapy, blood transfusion	Not specified

*Data presented in median
#Data presented in range

Table 3. Intervention detail.

First Author	Year	Experimental Group Intervention	Tea Preparation for Intervention	Intervention Dose	Duration of Therapy	Control Group Intervention	Timing of Laboratory Test
Soeizi[17]	2017	Green tea consumption, given after meals	2.5 g of green tea in 150 mL of hot water	Three times a day	8 weeks	Water regimen	Before and after the 8-week intervention period
Shahdadi[16]	2017	Green tea, after each main meal	2 grams of green tea in 200 mL of water for 5 minutes with a sugar cube	Three times a day	1 month	No intervention	Before and after the intervention
Petiwathayakorn[15]	2023	GTE tablets (50 mg EGCG equivalent) given 30 minutes before breakfast	Spray-dried GTE powder mixed with microcrystalline cellulose and compressed into tablets	50 mg EGCG equivalent per tablet, 1 tablet per day	2 months	Placebo tablets with the same shape, size, and color as GTE tablets	Blood samples were collected at the beginning of the study, after 1 month, and after 2 months
Badiee[14]	2015	Green tea infusion given before meals + DFO	6 g of GT in 200 mL of hot water (60–70°C), cooled at room temperature for 5 min	12 g/day	1 month	Regular chelation therapy with DFO	Blood samples were collected immediately before and 1 month after green tea administration
Al-Momen[13]	2020	Green tea (3 cups/day after meals)	Green tea bags (2 grams of Camellia sinensis)	Three cups a day	12 months	Usual treatment	Baseline and 12 months

Abbreviations: GTE = Green tea extract; DFO = Deferoxamine; EGCG = Epigallocatechin gallate.

DISCUSSION

This study reviewed and summarized the results of several interventional studies. Despite the significant number of studies identified during the preliminary screening, the quality of these studies varied considerably. The results indicated that green tea extract (GTE) supplementation can reduce serum iron and serum ferritin levels in transfusion-dependent thalassemia (TDT) patients. However, serum total iron-binding capacity (TIBC) and transferrin saturation were found to be insignificantly correlated with GTE supplementation. These findings are particularly beneficial for patients with major thalassemia who undergo routine transfusions and are continuously at risk of iron overload.

Green tea extract contains various phenolic compounds, such as tannins and catechins, which inhibit iron absorption in the intestinal lumen. The primary catechin found in green tea is epigallocatechin-3-gallate (EGCG), which has a wide range of benefits beyond its role as an iron chelator, including antioxidant and anti-inflammatory properties.[7,18] EGCG can inhibit intestinal iron absorption by reducing the basolateral transport of iron in intestinal luminal cells.[17,19] This mechanism is particularly relevant for TDT patients, who are at risk of iron overload due to repeated blood transfusions. The ability of catechins to chelate iron not only reduces its absorption but may also impact systemic iron homeostasis by modulating hepcidin levels, a key regulator of iron metabolism.[20] Additionally, catechins have hepatoprotective effects by scavenging reactive oxygen species, which are abundantly produced as byproducts of metabolism in hepatocytes. In thalassemia, the high rate of erythrocyte turnover leads to iron accumulation, which induces free radical formation through the Fenton reaction.[21] Furthermore, EGCG has been shown to reduce the expression of erythroferron (ERFE) in major thalassemia patients. ERFE typically increases as a compensatory response to chronic anemia due to ineffective erythropoiesis, and it represses hepcidin, thereby increasing iron mobilization into circulation.[22]

One of the main indicators of iron overload in TDT is serum ferritin, which has been negatively correlated with green tea supplementation. Nanri, *et al*., reported a similar negative association between green tea consumption and serum ferritin levels in men and pre-menopausal women; however, they noted a nonsignificant association in post-menopausal women.[23] Similarly, Sung, *et al*., found no significant correlation between tea consumption and serum ferritin levels.[24] The type of tea consumed and the timing of consumption may influence these associations. For instance, green tea contains higher levels of phenolic and flavonoid compounds compared to black tea, as the fermentation process in black tea production reduces its polyphenol content.[25,26] Additionally, consuming green tea after meals may enhance its effectiveness as an intestinal iron chelator, thereby reducing luminal iron absorption. In post-menopausal women, decreased circulating estrogen levels can induce hepcidin expression in hepatocytes, which reduces intestinal iron absorption and inhibits the release of stored iron, potentially masking the effects of green tea supplementation.[23] These factors must be

considered to optimize the effects of green tea supplementation.

Chronic inflammation, often present in patients with TDT, can significantly alter iron metabolism. Inflammatory cytokines can induce hepcidin production, leading to decreased iron absorption and mobilization from stores.[23] This interplay between inflammation and iron metabolism suggests that the effectiveness of GTE may be influenced by the inflammatory status of the patient. Future studies should investigate the potential of GTE to modulate inflammatory markers and its subsequent effects on iron metabolism.

The variability in age and gender among study participants may also affect the outcomes of GTE supplementation. Hormonal differences, particularly in premenopausal and postmenopausal women, can influence iron absorption and metabolism.[27] Additionally, age-related changes in gastrointestinal physiology may alter the absorption of dietary components, including GTE. Therefore, stratifying results based on these demographic factors could yield more tailored insights into the efficacy of GTE in different patient populations.

The potential interactions between GTE and existing treatments for TDT, such as iron chelation therapy, warrant further exploration. Combining GTE with standard therapies may enhance the overall management of iron overload; however, this requires careful consideration of possible interactions and cumulative effects on iron status.[28] Understanding these interactions could lead to more effective treatment protocols that incorporate dietary interventions alongside pharmacological therapies.

We acknowledge several limitations in this study. The primary limitation of this systematic review is the lack of high-quality studies with control groups. More high-quality randomized controlled trials (RCTs) are needed to provide better outcomes and reduce variability. Additionally, the age of subjects varied across the studies reviewed, leading to the assumption that the effects of GTE can be generalized across all age groups; however, we cannot specifically analyze the effects within each age group. The interventions relied on participant compliance with the protocol, which introduces potential exposure bias, despite several methods employed to mitigate this, such as weekly monitoring by phone and counting the remaining teabags after the intervention period. Future studies should involve larger sample sizes, consider various comorbidities, and extend the duration of interventions to yield higher-level evidence outcomes.

CONCLUSION

This study analysed and summarized the iron status of transfusion-dependent thalassemia patients who received green tea supplementation. There was an improvement in iron status by reduced serum ferritin and serum iron after green tea supplementation. However, the lack of high-quality studies with a wide range of subjects' ages and several confounding factors has to be considered. More homogeneous studies are needed to reduce the confounding factors and further analyse the association in various age groups.

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