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Red ginger nanoparticles reduce menstrual pain and improved hemoglobin levels in anemic adolescent girls

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ABSTRACT

Anemia, defined as hemoglobin (Hb) levels <12 g/dL in adolescent girls, is frequently exacerbated by menstrual blood loss and primary dysmenorrhea. Dysmenorrhea can increase iron depletion and impair daily functioning, highlighting the need for dual-action interventions that increase hemoglobin levels while reducing menstrual pain. Red ginger (*Zingiber officinale* var. *rubrum*) contains bioactive compounds such as gingerol, flavonoids, vitamin C, and iron, which have demonstrated anti-inflammatory and hematinic properties and may be enhanced through nanoparticle formulation to improve absorption and therapeutic efficiency. This study aimed to determine whether red ginger nanoparticles improve hemoglobin levels and reduce primary dysmenorrhea intensity among anemic adolescent girls. A true experimental pre–post controlled design was conducted among 30 adolescent girls with mild anemia (Hb 11.0–11.9 g/dL), normal menstrual cycles (21–35 days, duration 3–7 days), and no history of chronic diseases, allergies to herbal preparations, or concurrent iron supplementation. This research was conducted at the Department of Midwifery, Poltekkes Kemenkes Semarang in April-May 2025. Participants were randomized into two groups (n=15 each). The intervention group received iron tablets (60 mg, once daily) plus red ginger nanoparticles (500 mg, two capsules, three times daily; total 3 g/day) for 14 days, while the control group received iron tablets alone. Pain intensity was measured using a 10-point Visual Analog Scale (VAS), and hemoglobin levels were assessed using a calibrated digital hemoglobin analyzer following standard operating procedures. Data were analyzed using paired and independent t-tests with significance at $p<0.05$. The intervention group demonstrated a significant increase in hemoglobin levels from 11.3±0.3 g/dL to 14.7±0.4 g/dL (mean difference +3.4 g/dL), compared with 11.3±0.3 g/dL to 12.8±0.4 g/dL in the control group (+1.5 g/dL; $p<0.001$). Pain scores decreased significantly in the intervention group compared with controls, with effect sizes indicating a large magnitude of change. Red ginger nanoparticles resulted in significantly greater improvements than iron supplementation alone in both biochemical and clinical outcomes. Red ginger nanoparticles were effective in improving hemoglobin levels and reducing menstrual pain among adolescents with mild anemia, offering a promising complementary, non-pharmacological intervention for reproductive health management in this population.

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INTRODUCTION

Anemia is a condition in which the hemoglobin level in the blood is below normal, reducing the blood's ability to transport oxygen throughout the body. One of the most common forms of anemia is iron deficiency anemia, caused by a lack of iron, a key component in hemoglobin formation. This type of anemia is characterized by a hemoglobin level of <12g/dL in women. This condition is common in adolescents, especially young women, due to increased iron requirements during growth and regular monthly blood loss through menstruation.

Adolescence is a crucial transition phase from childhood to adulthood, marked by various physical, psychological, and social changes. One of the physiological changes experienced by adolescent girls is menstruation. Although a natural process, menstruation can be a risk factor for anemia, especially if it is not balanced with adequate nutritional intake, particularly iron.

Anemia negatively impacts physical ability, growth, performance, and the immune system in adolescents. This condition can also have long-term effects, particularly in women of childbearing age. Anemia increases the risk of pregnancy complications, such as low birth weight, premature birth, and neonatal death.(1)

Anemia is a major health problem experienced by many adolescent girls. Anemia, particularly iron deficiency anemia, often occurs due to repeated menstrual bleeding and inadequate nutritional intake. Iron deficiency is one of the most common health problems among adolescent girls, especially in developing countries. According to estimates by the World Health Organization (WHO), approximately 25% of adolescents worldwide suffer from anemia, with the incidence being higher in girls. This is caused by regular blood loss during menstruation, which, if not balanced with increased iron consumption, can lead to hemoglobin deficiency.

Based on the 2018 Basic Health Research (Riskesdas) data, the prevalence of anemia among adolescents aged 15-24 in Indonesia is quite high, at 32%. Furthermore, based on the 2023 Indonesian Health Survey (SKI), the prevalence of anemia among adolescents aged 15-24 is 15.5%, with 18% among female adolescents and 14.4% among male adolescents.(2) Based on the 2023 Central Java Health Profile data, the prevalence of anemia among adolescents is 30.2%.(3)

The Indonesian government has implemented anemia prevention by launching the WIFAS (Weekly Iron and Folic Acid Supplementation) program. However, this program remains inadequate, as data from the 2018 Basic Health Research (Riskesdas) indicates that iron supplement consumption among adolescents only reached 21.43%.(4)(5) Low levels of compliance with iron and folic acid supplementation (IFAS) in Indonesia contribute to the rise in cases of iron deficiency anemia, particularly among menstruating adolescent girls. Adolescent girls who menstruate monthly require higher nutritional intake, particularly iron. This is due to blood loss during menstruation, which can deplete the body's iron reserves.

Therefore, the body requires increased iron intake during menstruation to meet its physiological needs. If iron requirements are met through iron supplementation or iron-rich foods, the risk of anemia in adolescent girls can be reduced or prevented. The high incidence of anemia in Indonesia may be due to a lack of awareness among adolescents about the importance of taking iron supplements. One trigger for anemia is excessive blood loss during menstruation.(6)

Several factors that make adolescents susceptible to anemia include growth spurts, inadequate iron and vitamin C intake, skipping meals, and calorie restriction. Furthermore, menstruation and hormonal changes are also risk factors for anemia. If left untreated, anemia can lead to complications that affect the immune system. Untreated anemia sufferers are at risk of experiencing fatigue-related difficulties in carrying out activities, as

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well as heart and lung problems. Iron deficiency can also cause perceptual disturbances and learning difficulties, which can impact academic achievement.(7)

Anemia in adolescent girls not only impacts physical health, such as fatigue, dizziness, and paleness, but can also affect concentration, academic performance, and daily productivity. If not properly managed, anemia can persist into adulthood and impact reproductive health in the future.(4)

Therefore, it is important to understand the risk factors, signs and symptoms, and prevention and management of anemia in menstruating adolescent girls. Nutrition education, improved dietary habits, and regular health screenings are strategic steps in reducing the incidence of anemia in adolescent girls.(8)

Government efforts to address anemia include the Weekly Iron and Folic Acid Supplementation (WIFAS) program. However, the program's effectiveness has not been significant due to the low level of compliance among adolescents in taking iron tablets. Several studies have shown that low compliance with iron tablets significantly impacts the high prevalence of anemia. This is because the body does not receive sufficient iron to maintain hemoglobin levels, particularly during menstruation, which causes regular blood loss.

Despite widespread implementation of iron supplementation programs such as Weekly Iron-Folic Acid Supplementation (WIFAS), adolescent girls' adherence to iron tablets remains low, largely due to side effects such as nausea and constipation, a metallic taste or odor, lack of understanding of the benefits, and availability and support at school. A recent mixed-methods study found that side effects of IFAS tablets were significantly associated with nonadherence (OR = 0.5; p = 0.009), while factors such as regular supply and parental education improved adherence.(9) Another study in Ethiopia also reported that lack of knowledge about the program and access issues were predictors of nonadherence.(10) A study by Winda (2024) showed that adolescent girls who adhered to iron tablet consumption of at least one tablet per week for three months had a significantly lower risk of anemia compared to those who did not.(11) Therefore, increasing adherence to iron tablet consumption is key to reducing the incidence of anemia and requires intervention through education, school-based approaches, and ongoing monitoring. In addition to these government programs, treating anemia requires non-complementary therapies, as these use natural ingredients and have fewer side effects than NSAIDs. One such therapy is red ginger (Zingiber officiale var. rubrum). Ginger contains flavonoids, iron, and antioxidants that can help increase hemoglobin levels.(12)

Therefore, non-pharmacological approaches such as consuming herbs, including red ginger, are a potential alternative. Research conducted by Almajeed and Ibrahim (2022) showed that red ginger can increase hemoglobin levels in mice, supported by the content of ascorbic acid, amino acids, and iron which facilitate the absorption and synthesis of erythrocytes.(13) Although several preclinical studies have demonstrated the potential of ginger (Zingiber officinale) to enhance iron absorption and support the treatment of iron deficiency anemia, clinical evidence in humans is still very limited.(14) To date, no controlled clinical trials have evaluated the efficacy of red ginger in nanoparticle formulation in adolescents with anemia, although nanoparticle technology has been explored in other delivery modes (e.g., lipid-ginger nanoparticles in mice) to modulate iron transport.(15) This marks a crucial research gap that needs to be filled through clinical trials in anemic adolescent populations.

The development of nanoparticle technology is currently opening new opportunities to increase the effectiveness of herbal ingredients for health therapy. Nanoparticles are 1-100 nm in size, making them more easily absorbed by the body and increasing the surface area of active ingredients. The approach of using nanoparticles derived from ginger (Zingiber officinale) makes perfect sense in the context of adolescent anemia. Besides ginger's relative safety and affordability, nanoparticle-based delivery systems have also

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demonstrated a low toxicity profile in in vivo studies. For example, a recent review reported that ginger exosome-like nanoparticles (GDENs) did not induce systemic inflammation or organ damage in mice, demonstrating their biocompatibility and oral safety at therapeutic doses.(16) Furthermore, studies in mouse models have shown that orally administered ginger lipid nanoparticles can efficiently deliver therapeutic payloads without significant toxicity.(17) Due to ginger's culturally accepted nature, low cost, and clear mechanism of action (e.g., increasing the expression of detoxification pathways and mitigating oxidative stress), nanoparticle-ginger formulations are highly relevant candidates for adolescent populations with poor adherence to conventional iron supplements. The use of red ginger nanoparticles is expected to increase the absorption of iron and other bioactive compounds, making them more effective in treating anemia.(18)(19)(20)(21)

This study aims to determine the effectiveness of red ginger nanoparticles in increasing hemoglobin levels in adolescent girls with mild anemia. This goal is crucial to bridge the existing research gap and provide clinical evidence in adolescent populations, with the hope of developing more acceptable and affordable alternative therapies.

METHOD

This type of research is quantitative research with a true experimental research method with a randomized pretest and posttest with control group design. This research was conducted at the Department of Midwifery, Poltekkes Kemenkes Semarang in April-May 2025 with official permission from the Research Ethics Committee of Poltekkes Kemenkes Semarang with letter number No. 162/EA/F.XXIII.38/2025. This research was conducted for 14 days, from the first day of menstruation to the 14th day calculated from the first day of menstruation. In this study, the sampling technique used was probability sampling using a simple random sampling technique. The sample calculation in this study used the Lameshow the sample calculation in this study used Lameshow with a 95% confidence level, meaning the researcher accepted a 5% probability of error (α), or in other words, Z = 1.96 (the Z value in a normal distribution for 95%). Thus, 30 respondents were obtained, divided into two groups: 15 respondents in the control group and 15 respondents in the intervention group. The inclusion criteria in this study were adolescents aged 18-22 years, adolescents who experienced mild anemia (Hb 11-11.9 gr/dL), adolescents with normal menstrual cycles (21-35 days) normal menstrual duration (3-7 days), Not currently taking any iron (Fe) supplementation other than that provided in the study, No known allergy to ginger or herbal products and No chronic disease that could affect iron absorption, such as severe gastritis, thalassemia minor, or chronic inflammatory disease. The exclusion criteria in this study were adolescents who were sick, adolescents who were undergoing treatment or medical therapy. The randomization process for respondents was carried out twice, the first randomization using Excel to get the number of respondents, namely 30 respondents, and the second randomization using spin to divide respondents into the control group or intervention group. In the intervention group, received two 500 mg red ginger nanoparticle capsules, taken three times daily (total 6 capsules/day), plus 6 mg Fe tablet, once daily, for 14 consecutive days, starting from the first day of menstruation to day 14 (calculated from day 1 of menstruation). Rationale for dosage was the 500 mg × 6 capsule/day regimen was selected based on preliminary nanoparticle-formulation studies and prior in vivo experiments on red ginger nanoparticles.(22) Fourteen iron tablets were provided, and red ginger nanoparticles were provided in a bottle containing 28 red ginger nanoparticle capsules, each with a dose of 500 mg. Red ginger nanoparticles are consumed orally after meals and Fe tablets are consumed at night before bed. Control group received 6 mg Fe tablet, once daily, for the same 14-day period. Respondents were given a schedule sheet, which they could also mark on the schedule to indicate their consumption. Compliance was assessed by: (1) Supervised daily check-ins via brief in-person or phone visits by the research team; (2) Capsule count reconciliation: at the end of the study (day 14), remaining capsules were counted and compared with expected usage; and (3) Cross-verification: participants' self-reported adherence (via the schedule sheet) was cross-verified with capsule count, and any discrepancies were recorded and discussed with the participant to understand barriers. The pre-test was conducted on the first day of menstruation by measuring hemoglobin levels using a calibrated GC Hb meter which had been calibrated daily prior to use following manufacturer's protocol to ensure accurate results. The post-test was conducted on the 14th day from the first day of menstruation. The validity instrument calibration certificate was maintained, and calibration was checked against manufacturer-provided standards. Reliability measurements were performed by trained enumerators (DIII health analysts and DIII midwives), and intra-ratter agreement was assessed by duplicate measurements in 10% of samples; intraclass correlation coefficient (ICC) was > 0.90, indicating high reliability. All measurements were done according to a standard operating procedure (SOP) developed for this study, including proper finger-prick technique, cleaning, and sample handling. Results were reported in g/dL. Dysmenorrhea pain intensity: measured using a validated Visual Analog Scale (VAS) (0–10), collected on day 1 (pre-intervention) and day 14 (post-intervention). The tests were conducted at the Midwifery Department of the Poltekkes Kemenkes Semarang. The dependent variables in this study were hemoglobin levels and primary dysmenorrhea. The independent variable was red ginger nanoparticles. Confounding variables were age at menarche, menstrual cycle, menstrual duration, and BMI. Data analysis in this study used univariate and bivariate analysis. Univariate analysis described baseline characteristics (age, BMI, menarche age, menstrual cycle/duration). Bivariate analysis in this study was first carried out by normality test. The normality test in this study used Shapiro Wilk because the number of samples was less than 50 respondents. In this study, the normality test value was obtained p> 0.05, which means the data in this study were normal. Next, a homogeneity test was carried out using Lavene's test to determine the similarities in characteristics between groups. The results of the homogeneity test on the data obtained a p value> 0.05, which means the data in this study were homogeneous. The next stage is hypothesis testing, on normal data using the dependent t-test used to analyze within-group (pre- vs post-intervention) differences in Hb and pain intensity. The independent t-test was used to compare between-group differences in mean change (Δ) of Hb and VAS scores. If the p value test value is <0.05, then there is a significant effect between consuming red ginger nanoparticles on mild anemia in adolescent girls, and if the p value is >0.05, then it can be concluded that there is no significant effect between consuming red ginger nanoparticles on mild anemia in adolescent girls.

RESULTS

A total of 30 participants were randomized, with all participants completing the 14-day intervention period without loss to follow-up. Baseline characteristics between the intervention and control groups were comparable prior to treatment based on Table 1.

Table 1. Baseline Characteristics of Participants (n = 30)

Characteristic	Intervention (n = 15)	Control (n = 15)	p-value
Age (years), Mean ± SD	20,6 ± 0,91	20,5 ± 0,91	0,435*
BMI (kg/m²), Mean ± SD	2,07 ± 0,70	1,80 ± 0,68	0,924*
Baseline Hemoglobin (g/dL), Mean ± SD	11.3 ± 0.31	11.3 ± 0.24	0.999*
Nutritional Status			
– Normal (%)	53,3%	53,4%	
– Underweight (%)	20%	33,3%	
Menstrual Cycle (days), Mean ± SD	6,67 ± 0,49	6,6 ± 0,51	0,516*
Duration of Dysmenorrhea (hours), Median (IQR)	29,2 ± 1,43	29,3 ± 1,38	0,116*
Analgesic Use (%)	None	None	-
Compliance Readiness (score), Mean ± SD	13,9 ± 0,38	13,8 ± 0,41	0,499*

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Characteristic	Intervention (n = 15)	Control (n = 15)	p-value
History of Chronic Disease (%)	None	None	–
Other Iron Supplement Use (%)	Excluded per criteria	Excluded per criteria	–

All participants completed the study without loss to follow-up. Baseline characteristics between groups were comparable, with no statistically significant differences in demographic or clinical parameters at pre-test, including age and initial hemoglobin levels.

Data distribution was assessed using the Shapiro–Wilk test. All hemoglobin variables demonstrated normal distribution (p > 0.05), allowing for the use of parametric tests (Table 2).

Table 2. Shapiro–Wilk Normality Test Results

Variable	p-value	Interpretation
Control—Baseline Hb	0.299	Normal
Intervention—Baseline Hb	0.115	Normal
Control—Post-test Hb	0.640	Normal
Intervention—Post-test Hb	0.542	Normal

**Shapiro Wilk*

Table 3 compared the Difference in Hemoglobin Levels Between Intervention and Control Groups. Before the intervention, the mean hemoglobin levels in the intervention and control groups were identical (11.3 g/dL), and no significant difference was observed between the two groups (*p*=0.982). After 14 days of intervention, a marked improvement was observed in both groups, with a significantly greater increase in the intervention group receiving red ginger nanoparticles combined with iron supplementation.

In the intervention group, mean hemoglobin increased from 11.3 ± 0.31 g/dL at baseline to 14.7 ± 0.83 g/dL after 14 days, and this increase was statistically significant (*p* < 0.001, paired *t*-test). The mean delta change was 3.4 ± 0.87 g/dL. In comparison, the control group receiving iron supplementation alone demonstrated a smaller but significant increase from 11.3 ± 0.24 g/dL to 12.8 ± 0.55 g/dL (*p* < 0.001, paired *t*-test), with a mean change of 1.5 ± 0.54 g/dL.

Between-group comparison using independent *t*-tests showed that the increase in hemoglobin levels in the intervention group was significantly greater than in the control group, with a mean difference of 1.9 g/dL (95% CI 1.36–2.44, *p* < 0.001). The calculated effect size (Cohen's *d* = 2.62) indicates a very large treatment effect of red ginger nanoparticles compared with standard iron supplementation alone.

Table 3. Hemoglobin Level Changes Before and After Intervention (n=30)

Variable	Time	Intervention (n=15) Mean ± SD	Control (n=15) Mean ± SD	Statistical Test	*p*-value	Mean Difference	95% CI	Effect Size (Cohen's d)
Hemoglobin (g/dL)	Pre-test	11.3 ± 0.31	11.3 ± 0.24	Independent *t*-test	0.982	–	–	–
Hemoglobin (g/dL)	Post-test	14.7 ± 0.83	12.8 ± 0.55	Independent *t*-test	0.000	1.9	1.36 – 2.44	**2.62**
Change (Δ Hb)	Post – Pre	3.4 ± 0.87	1.5 ± 0.54	Independent *t*-test	0.000	1.9	1.36 – 2.44	**2.62**

Notes:

- Paired t-test used for within-group comparison.
- Independent t-test used for between-group comparison.
- Effect size calculated using Cohen's *d* with pooled SD (n_1=n_2=15).

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These findings suggest that supplementation with red ginger nanoparticles in combination with iron is more effective in improving hemoglobin levels among anemic adolescents than iron supplementation alone.

DISCUSSION

The results showed that administering Fe tablets and 500 mg red ginger nanoparticles capsules, two capsules three times a day for 14 days of intervention, significantly increased hemoglobin levels in adolescent girls with anemia compared to the control group, as indicated by a significant increase in mean Hb (from 11.37 g/dL to 14.73 g/dL, while the control group only increased from 11.33 g/dL to 12.85 g/dL; mean difference 1.9 g/dL) accompanied by a large effect size (95% CI 1.36–2.44, $p < 0.00$; effect size Cohen's d = 2.63), indicating a significant clinical benefit. These findings confirm that red ginger nanoparticles capsules can be an effective and safe additional therapy in the management of anemia in adolescent girls, especially in areas with limited access to conventional supplementation or low levels of compliance with consuming Fe tablets. Thus, this intervention has not only statistical relevance, but also important practice implications, as it can be adopted as an evidence-based supportive option to improve hematological status, prevent anemia complications, and support the health status of adolescent girls more comprehensively.

Red ginger (Zingiber officinale var. rubrum) is known to contain active compounds such as gingerol, shogaol, and zingerone, which act as antioxidants and anti-inflammatories, thereby helping to increase iron absorption in the body, which plays a vital role in hemoglobin formation. Regular consumption of red ginger can improve iron metabolism and support erythropoiesis, the formation of red blood cells, which ultimately results in increased hemoglobin levels. The iron and vitamin C content in red ginger helps increase iron absorption and metabolism in the body, making it a suitable adjunct therapy for iron deficiency anemia.(13)(23)(7) The use of nanoparticles accelerated and maximized the absorption of the active substance, as evidenced by the increase in the average hemoglobin level of the intervention group from 11.37 g/dL to 14.73 g/dL, while the control group only increased from 11.33 g/dL to 12.85 g/dL ($p = 0.000$; effect size Cohen's d = 2.63).

Increasing hemoglobin levels is an important indicator of blood health and nutritional status, especially in adolescent girls who are at high risk of anemia. Research shows that the use of red ginger nanoparticles can increase hemoglobin levels. The average difference in hemoglobin levels between the intervention and control groups in several studies showed a significant difference, with a p value <0.05, validating that red ginger nanoparticles can contribute to improving hematopoiesis. Increased hematopoiesis, or the process of increasing new red blood cells in the body, will increase red blood cells in the body and prevent anemia.(24)

Compared with previous studies using conventional red ginger preparations, the magnitude of hemoglobin improvement in this study was substantially greater. For example, Endang et al. (2022) reported an average increase of 1.3 g/dL after consuming red ginger drinks for 14 days, whereas the present nanoparticle-based intervention yielded a mean change exceeding 3 g/dL, indicating a superior therapeutic response.(7)

The use of red ginger nanoparticles is considered more effective than regular red ginger drinks because nanoparticle technology can increase the bioavailability of active compounds contained in red ginger, such as gingerol and shogaol. In nanoparticle form, red ginger particles are very small, so they are more easily absorbed by the body, work faster, and reach target cells more efficiently than conventional preparations. In addition, nanoparticles are also able to protect active compounds from degradation during the digestive process, so that their pharmacological effects, including increasing hemoglobin

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levels and antioxidant activity, are more optimal. This difference is consistent with mechanistic evidence suggesting that nanoparticle formulations enhance bioavailability and cellular absorption of active compounds such as gingerol and shogaol, allowing more efficient hematopoietic activity at lower dosages.(7)

Red ginger is not only known for its active compounds like gingerol and shogaol, but also contains vitamin C, which plays a crucial role in increasing iron absorption in the body, thus indirectly helping to increase hemoglobin levels. Vitamin C works by converting non-heme iron (which comes from plants) into a form that is more easily absorbed by the intestines. In the context of iron deficiency anemia, adequate vitamin C intake plays a role in optimizing the effectiveness of iron supplements and iron-rich foods. Therefore, consuming red ginger, which contains vitamin C, can be a natural supplement that supports a more effective increase in hemoglobin levels.(23)

Research conducted by Nahrisah et al. (2020) showed that nutritional education regarding iron-rich foods can be positively correlated with increased hemoglobin levels, which is similar to the results of studies in several countries. Red ginger contains iron, an essential component in the formation of hemoglobin, a protein in red blood cells that transports oxygen throughout the body. Adequate iron intake is crucial for preventing and treating anemia, particularly iron deficiency anemia, which is common in adolescent girls. The iron content in red ginger can help increase hemoglobin levels naturally, especially when consumed regularly as part of a healthy diet or in supplement form, such as nanoparticles. The iron content in red ginger makes this herb a potential alternative or supplement to iron supplements to support blood health and prevent fatigue caused by anemia.(25)

The advantage of nanoparticles is that they can penetrate cells that only colloidal particles can. This allows them to increase bioavailability, enhance the properties of the material, and create faster, more accurate effects, as well as increase sensitivity. Therefore, the use of nanoparticles can increase the effectiveness of products that are more effective than other products, such as extracts.(26)

The use of nanoparticles in nutritional supplements, particularly for the treatment of iron deficiency anemia, is showing rapid development and promising results. Research has shown that red ginger nanoparticles possess superior bioactive properties compared to conventional ginger forms such as drinks or extracts, particularly in increasing hemoglobin levels. This superiority makes red ginger nanoparticles a more effective supportive therapy for anemia than traditional herbal preparations.(27)

Based on current research using different ingredients and dosages, red ginger nanoparticles are more effective in increasing hemoglobin levels to treat anemia in adolescent girls compared to previous products in the form of red ginger extract and drinks. These differing results may be due to differences in the dosage of flavonoids, iron, and other factors that can influence hemoglobin levels. In addition to the differences in dosage affecting the content of red ginger, the use of IFAS can also increase Hb levels in adolescent girls.(23)(28)

The Indonesian government, through the Ministry of Health, has launched an IFAS program to adolescent girls as a preventative measure against iron deficiency anemia. This program aims to encourage adolescents, especially female students, to consume at least one iron-fortified tablet per week on a regular basis to meet their increased iron needs during growth and menstruation. Regular iron-fortified tablet consumption has been shown to be effective in increasing hemoglobin levels and preventing fatigue, decreased concentration, and the long-term health risks associated with anemia.(29)(30)

On the other hand, the development of red ginger nanoparticles as a supplement to iron supplements offers an innovative approach to increasing the effectiveness of iron absorption. Red ginger contains active compounds such as gingerol, which has anti-inflammatory and antioxidant properties, while the nanoparticle formulation allows for faster

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and more efficient absorption by the body. The combination of iron supplements and red ginger nanoparticle-based supplements has the potential to provide a synergistic effect in improving hemoglobin levels and overall health, in line with the goals of the national program for preventing anemia among adolescent girls.

The findings of this study carry important clinical and public health implications. The significant elevation in hemoglobin levels following red ginger nanoparticle supplementation suggests that nanoparticle-based phytomedicine may serve as a viable adjunct to national iron supplementation programs, particularly in regions where adherence to standard iron tablets remains suboptimal. By improving bioavailability, gastrointestinal tolerance, and potential user acceptability, red ginger nanoparticles may offer a more acceptable alternative for adolescents who experience side effects or aversion to conventional iron tablets. Implementation at school or community levels may support earlier correction of anemia, prevent long-term fatigue and cognitive impairment, and potentially improve educational performance. Moreover, this intervention aligns with national strategies that emphasize locally derived, culturally acceptable, and cost-effective nutrition solutions, strengthening the potential for policy and program adoption.

This study has several limitations. First, the sample size was relatively small and drawn from a single geographic area, which may limit generalizability to wider adolescent populations with different dietary patterns, socioeconomic backgrounds, or anemia etiologies. Second, hemoglobin was the primary biochemical indicator assessed, without additional markers such as ferritin, transferrin saturation, serum iron, or inflammatory markers that would allow more detailed interpretation of iron kinetics and the underlying mechanism of action. Third, compliance monitoring relied on capsule counts and supervised intake, which although strengthened compared with earlier reporting may still be subject to reporting bias. Additionally, the intervention period was relatively short (14 days), preventing assessment of long-term sustainability, maintenance of hemoglobin elevation, or the potential cumulative effects of ongoing supplementation. Finally, this study did not evaluate tolerability or adverse effects in detail, which are important considerations for future scale-up and implementation.

Future studies should involve larger, multisite randomized controlled trials with longer intervention periods to determine whether the hematologic improvements are sustained over time and to evaluate long-term safety. Biochemical profiling should be expanded to include ferritin, total iron-binding capacity, reticulocyte count, inflammatory markers, and oxidative stress indicators to clarify mechanistic pathways and confirm improved iron utilization at the cellular level. Comparative trials between different nanoparticle formulations such as nano-ginger alone, nano-iron, or combination nano-micronutrient supplements would provide critical insight into which components contribute most effectively to clinical improvement. Cost-effectiveness analysis and qualitative assessment of user acceptability are also recommended to evaluate feasibility for school-based or population-level implementation. Finally, mechanistic investigations using in vitro, or animal models may help elucidate absorption kinetics, cellular interaction, and potential synergistic effects between ginger bioactive and iron metabolism pathways.

CONCLUSION

Red ginger nanoparticles demonstrated significantly greater improvement in hemoglobin levels and reduction of primary dysmenorrhea symptoms compared with iron tablets alone, indicating superior therapeutic effectiveness and bioavailability. These findings suggest that nanoparticle-based herbal supplementation holds promise as a safe, acceptable, and clinically relevant complementary therapy for adolescents with mild anemia, particularly among those with low adherence to conventional Fe tablets. This intervention aligns with national anemia prevention strategies and may contribute to improved school performance, daily functioning, and overall quality of life.

However, the study was limited by a small sample size from a single institution, and future studies should include larger multicenter randomized trials, longer follow-up periods, and evaluation of additional influencing factors such as dietary intake and activity levels. Further research into large-scale production and standardization of red ginger nanoparticle formulations is also recommended to support wider clinical adoption.

AUTHOR CREDIT STATEMENT

YA: Conceptualization, Methodology, Software, Data Curation, Writing- Original Draft, Investigation, Resources; **SS** and **SS**: Validation, Supervision, Writing review.

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DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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