Food Research 7 (Suppl. 1) : 111 - 117 (2023)
Journal homepage: https://www.myfoodresearch.com

FOOD RESEARCH

FULL PAPER

Efficacy of soy biopeptide on serum iron, serum ferritin and hemoglobin levels of adolescent girls in Pandeglang district in Indonesia

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Article history:
Received: 2 March 2022
Received in revised form: 29 April 2022
Accepted: 4 October 2022
Available Online: 27 April 2023

Keywords:
Soy-biopeptides,
Serum iron,
Serum ferritin,
Hemoglobin

DOI:
https://doi.org/10.26656/fr.2017.7(S1).20

Abstract

Soy hydrolysate contains biopeptides that can increase the absorption of iron. The study aimed to analyze the efficacy of a Soy-biopeptide in improving serum iron, serum ferritin and hemoglobin among female adolescents. For the product's efficacy study, a one-group pre-test—post-test design was conducted. The products were given every day for 14 days. The serum iron, serum ferritin and hemoglobin were measured twice prior to administration and after day 14, for 52 respondents of female adolescent girls who met the inclusion criteria. The results showed that serum iron levels increased significantly from (66.87±32.44) mcg/dl to (103.77±55.87) mcg/dl (p = 0.000) in both groups. Meanwhile, serum ferritin levels increased significantly in the group with serum ferritin levels from (13.29±9.5) ng/ml to (17.48±12.18) ng/mL (p = 0.00), but there was no significant change in the group with serum ferritin levels from (28.06±23.7) ng/ml to (29.05±21.3) ng/ml (p = 0.64).The respondent's hemoglobin level before administration was (12.21±1.29) g/dl and did not change significantly after administration (12.05±1.31) g/dl (p = 0.016). In conclusion, soy-biopeptide has the health benefits of increasing serum iron and serum ferritin levels in respondents with low iron intake and can maintain normal hemoglobin levels.

1. Introduction

Anemia is a serious health problem whose prevalence worldwide according to WHO reaches 2.3 billion people and is generally experienced by women and children (United Nations Sub-Committee on Nutrition (ACC/SCN), 2000). Iron deficiency is the main cause of anemia, where blood hemoglobin levels are below normal levels (Camaschella, 2015). Anemia due to iron deficiency is still one of the main national health problems that get serious attention from the government because prevention is quite difficult, takes a long time and is very expensive.

In Indonesia, iron deficiency anemia occurs in almost all age groups. Data for Basic Health Research (Riskesdas) in 2018 (Kementerian Kesehatan RI, 2018) showed that the prevalence of anemia in adolescent girls was 32% and in pregnant women was around 48.9%. Meanwhile, the prevalence of anemia in women of childbearing age (aged 15-49 years) is 31.2% (WHO, 2019). Low iron intake, especially in children, can lead to growth disorders (stunting), menstrual pattern disturbances in adolescents, difficulty thinking and concentrating, decreased intelligence and endurance, susceptibility to infectious diseases (Lopez *et al.,* 2016), and can even increase risk of maternal and child mortality, as well as in infants resulting in low birth weight.

The Ministry of Health Indonesia sets the value of the nutritional adequacy rate (RDA) for iron for children aged 10 -12 years at 20 mg/day, while for adolescent girls aged 13-18 years at 26 mg/day and women of childbearing age (15-44 years) at 26 mg/day (Kementerian Kesehatan RI, 2019), but in reality, the daily iron intake is much lower than the RDA value. On the other hand, adolescence is a period of rapid growth, where currently the peak of maximum growth occurs, causing very high nutritional needs. However, if iron intake during adolescence is lacking and lasts for a long time, then growth cannot take place optimally and can cause anemia. Iron deficiency in adolescence is also at risk for anemia in later pregnancy, so it is important to ensure adequate iron intake during adolescence.

Iron is a nutrient that has a role in producing hemoglobin, an important component in red blood cells that is responsible for delivering oxygen throughout the body (Putri *et al.,* 2020). Chronic iron deficiency and its

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eISSN: 2550-2166
Published by Rynnye Lyan Resources

limited absorption in the body (only 3-35% of Fe is absorbed from food), are some of the factors that cause impaired absorption of iron. In addition, several compounds in foodstuffs such as phytate, oxalate, polyphenols, milk protein, albumin and iron can also inhibit iron absorption. However, certain foodstuffs such as meat and ascorbic acid can help absorb iron (Dasa and Albera, 2018; Sun *et al*., 2020).

Several types of protein hydrolysate or bioactive peptides are reported to help iron absorption by forming iron-peptide complex bonds (iron chelation) to help iron absorption in the intestine (Li, 2017). In a previous study, soy protein hydrolysates obtained contained bioactive peptides using steam blasting and enzymatic hydrolysis techniques (Laily *et al*., 2014). This protein hydrolyzate has been tested for its ability to increase iron absorption in vitro and in vivo (Wijayanti *et al*., 2019; Susanti *et al*., 2019). This hydrolysate is then specially formulated and fortified with Fe, vitamins and minerals called Purula. The study aimed to analyse the efficacy of a biopeptide hydrolysate in improving the serum iron, serum ferritin and hemoglobin among female adolescents and to describe the readiness of a sample of urban Indonesian school communities to implement the adoption of a school-based nutritional intervention for adolescents. It is hoped that the results of this study can be the scientific evidence for the application of this product to prevent anemia, especially in young women.

2. Materials and methods

2.1 Product description

The product is a food supplement in the form of savoury flakes made from soybean hydrolysate, and seaweed, and fortified with iron and premixed vitamins. The product contains amino acids, di-, tri-, and polypeptides that can chelate iron (Table 1). The product contains biopeptides of less than 15 kDa (Laily *et al.*, 2014; Wijayanti *et al*., 2019). Each 10-gram sachet of product contains 4.3 g elemental iron and fulfils 40-50% of the iron RDA aged 9-18 years old (Kementerian Kesehatan RI, 2019). The current daily-recommended use is two sachets per day.

2.2 Study design

Efficacy study used a pre-experimental design, one group pre-test – post-test design conducted in October 2018. The research sites were in Panimbang and Cigeulis Districts, Pandeglang District, Banten Province The inclusion criteria in this study were young women aged 15-18 years. They should not have the habit of consuming coffee, tea, soft drinks, alcoholic beverages, or caffeine-contained drinks more than once per day. The respondents were also not on a diet program to lose weight and were not doing excessive exercise. While the exclusion criteria of research respondents were having a history of allergies to soy and soy-derived products, having a history of chronic disease/infection, not menstruating at the time of blood sampling, being vegetarian and having a BMI <17 or >27. Research respondents were selected using the purposive sampling

Table 1. Nutritional composition of Purula.

Name of Product	Parameter	Unit	Content Levels after supplementation with minerals and vitamins	
			Per serving (10 g)	Per daily consumption (two servings)
Purula 10 g, 2 servings per day	Total Energy	kcal	40.286	80.572
	Energy From fat	kcal	8.37	16.74
	Carbohydrate	g	6.432	12.864
	Sugar	g	1.247	2.494
	Protein	g	1.547	3.094
	Total Fat	g	0.93	1.86
	Fe (Elemental Iron)	mg	4.3	8.6
	Zn (Zinc)	mg	3.5	7
	Calcium	mg	3	6
	Iodium	µg	37.5	75
	Folate	µg	150	300
	Vitamin B 12 (Cyanocobalamin)	µg	0.6	1.2
	Vitamin B 1 (Thiamine)	mg	0.885	0.77
	Vitamin B 2 (Riboflavin)	µg	0.4	0.8
	Vitamin B 3 (Niacin)	mg	4.2	8.4
	Vitamin B 6 (Pyridoxin)	mg	0.42	0.84
	Vitamin C	mg	12	24
	Vitamin K	µg	14	28
	Sodium	mg	179.528	359.056

https://doi.org/10.26656/fr.2017.7(S1).20

method, where respondents are selected from young women who attend high schools in Pandeglang district and met the inclusion and exclusion criteria. Selected respondents must also have agreed to participate in this study by signing the Informed Consent. The number of respondents who took part in the study was 65 young women.

Sample products used in this study were given to respondents as much as 2 sachets per day for 2 weeks. The products were distributed daily by the appointed teacher in each school. Furthermore, the teacher monitors the daily respondent sample consumption by recording if there is a remaining daily sample that is not consumed by the respondent. The biochemical examination of blood done was serum ferritin levels, serum iron levels and haemoglobin before and after 2 weeks of intervention. Blood sampling and blood biochemical examination were carried out by experienced medical analysts from clinical laboratories. Blood samples were taken in the morning. Respondents were asked to fast at least 8 hrs before treatment. A biochemical examination of blood was carried out on the first day and day fourteen. The treatment was started on the first day.

2.3 Research Instrument, procedure, and data analysis

For the efficacy study, the type and amount of food consumed by respondents were obtained through interviews using a food recall form 1×24 hrs every week for the two weeks of treatment. Respondents were also interviewed about their eating habits using the Food Frequency Questionnaire form. Measurements of hemoglobin, serum ferritrin and serum iron levels were performed before and after the intervention for 14 days. The method used to measure hemoglobin levels was cyanmethemoglobin and oxyhaemoglobin (photometric test). Serum ferritin was measured using the immunochemiluminescent method (Imulit 2000), while serum iron was measured using a spectrophotometric method using Ferene (triazine breakdown ferrene). Data were analyzed using univariate and bivariate statistics using the IBM SPSS statistical software (SPSS 20) with a significant value of $p < 0.05$. The research was started after getting permission from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia.

3. Results

The initial number of participants who were willing to take part in the study was sixty-five respondents, but during the study there were thirteen respondents whose data were incomplete due to several reasons such as not being present at the time of the examination, moving residence or menstruating at the time of blood sampling after the intervention. The final number of respondents who completed the study was 52 adolescent girls. Table 2 shows the participants' characteristics for the efficacy study of products. Most of the participants had enough and good knowledge about anemia at 44.2% and 34.6%, respectively. Theparents' education level of the respondents was mostly low, both the mothers' and fathers' education were lower than highschool levels at 88.5% and 80.8%, respectively. More than half were coming from a family with low food consumption expenditure.

Table 2. Participants' characteristics for the efficacy study.

Variable		n	(%)
Knowledge about anaemia			
• Good	(True, ≥ 75%)	18	(34.6)
• Moderate	(True, 56%-75%)	23	(44.2)
• Low	(True, < 56%)	11	(21.2)
Mother's Education			
• ≥ graduated high school		6	(11.5)
• < high school		46	(88.5)
Father's Education			
• ≥ graduated high school		10	(19.2)
• < high school		42	(80.8)
Expenditures for consumption			
• High	(If ≥ 1.5 million IDR)	24	(46.2)
• Low	(If < 1.5 million IDR)	28	(53.8)

3.1 Characteristics of food intake from the 2×24 hours recall

Most of the respondents' iron intake during the intervention was not sufficient, as many as 84.6% of respondents did not meet the RDA (Table 3). Likewise, with protein intake, most of the respondents did not consume adequate amounts of protein (73.1%). More than half (51.9%) of respondents met the adequate intake of Vitamin B 12. On the other hand, most of the respondents did not meet the intake of vitamin C (98.1%), vitamin A (57.7%) and vitamin B6 (53.8%). There are no respondents who meet the adequate intake of iron and zinc. It is clear that the respondents lack intake of nutrients that play a role in the production of red blood cells.

Almost half (46.2%) of the respondents consumed iron tablets (182 mg ferrous fumarate and 0.400 mg folic acid), then in this study, the data analysis was separated into two groups (Table 4). The group that received folic acid iron supplementation every week (WIFAS) and the group that did not get folic acid iron supplementation every week (non-WIFAS).

There were no significant differences in serum ion, serum ferritin and haemoglobin between the two group.

https://doi.org/10.26656/fr.2017.7(S1).20

Table 3. Protein and micronutrient intake during the study period.

Variable		N	(%)
Protein			
Adequate	(≥ 80% RDA)	14	(26.9)
Low	(< 80% RDA)	38	(73.1)
Vitamin C			
Adequate	(≥ 100mg/day)	1	(1.9)
Low	(< 100mg/day)	51	(98.1)
Iron			
Adequate	(≥ 7 mg/day)	44	(84.6)
Low	(< 7 mg/day)	8	(15.4)
Zinc (Zn)			
Adequate	(≥ 80% RDA)	0	(0)
Low	(< 80% RDA)	52	(100)
Vitamin A			
Adequate	(≥ 80% RDA)	22	(42.3)
Low	(< 80% RDA)	30	(57.7)
Vitamin B6			
Adequate	(≥ 80% RDA)	24	(46.2)
Low	(< 80% RDA)	28	(53.8)
Vitamin B12			
Adequate	(≥ 80% RDA)	27	(51.9)
Low	(< 80% RDA)	25	(48.1)

However, the Serum Ferritin was higher in groups who received iron tablet (Table 5). After the 14 days of the biopeptide administration the serum iron, serum ferritin and Hemoglobin were measured. There was a significant increase in serum iron after the consumption of the product. The serum iron level increased significantly in all groups merged analysis, from (66.87±32.44) mcg/dl to (103.77±55.87) mcg/dl (p = 0.000). Despite both groups started with an equal level of serum iron in the start of the study, in the segregated analysis, the significant improvement only found in the group that did not receive any iron tablet from (66.92±36.15) mcg/dl to (108.89±55.75) mcg/dl (p = 0.000) (Table 6).

Table 4. Biochemical characteristics of respondent's blood before a treatment based on WIFAS and Non-WIFAS groups.

Variable	Non-WIFAS (N = 28)	WIFAS (N = 24)	Sig. P
Intital Serum Iron	66.93±36.15	66.79±28.27	0.988
Initial Serum Ferritin	13.30±9.47	28.06±23.68	0.08
Intitial Hemoglobin	12.06±1.26	12.39±1.33	0.355

*WIFAS = Weekly Iron Folic Acid Supplementation

The serum ferritin level increased significantly only in the group with no iron tablet (13.29±9.5) ng/mL to (17.48±12.18) ng/mL (p = 0.000). The group without iron tablet consumption started with lower serum ferritin levels, of less than half of the group who received iron tablets (Table 7).

Within two weeks of treatment, there was no

Table 5. Differences in food intake in the WIFAS and Non-WIFAS groups

Variable	N	Mean	SD	Min	Max	P value
Protein intake						
WIFAS	24	46.0167	12.50664	29.31	87.33	0.13
Non-WIFAS	28	41.1146	10.22882	21.54	63.83	
Fe intake						
WIFAS	24	9.6975	3.45692	4.76	22.90	0.199
Non-WIFAS	28	10.3618	3.29489	4.45	20.22	
Folate intake						
WIFAS	24	292.0525	147.3227	114.68	842.88	0.797
Non-WIFAS	28	281.2143	70.76239	93.30	432.62	
Zinc intake						
WIFAS	24	6.5571	1.6607	3.77	10.19	0.38
Non-WIFAS	28	6.1700	1.49825	3.45	8.81	
Vitamin B12						
WIFAS	24	3.1129	2.13231	0.88	9.17	0.03
Non-WIFAS	28	2.0436	1.01817	0.40	3.97	
Vitamin C						
WIFAS	24	39.7179	20.52128	11.93	86.05	0.673
Non-WIFAS	28	40.2471	19.33239	15.76	115.85	
Vitamin A						
WIFAS	24	500.4558	349.616	167.67	1940.60	0.898
Non-WIFAS	28	457.4046	219.9598	129.05	1217.55	

*WIFAS = Weekly Iron Folic Acid Supplementation

https://doi.org/10.26656/fr.2017.7(S1).20

significant increase in Hb level in all groups before and after the product administration (Table 8). However, in the group of respondents with Hemoglobin levels less than 12.0 g/dl, there was a significant increase in serum ferritin after the product intervention for 2 weeks (Table 9).

Table 6. Serum iron levels before and after administration of the WIFAS and Non-WIFAS groups

Groups	Variable		N	P-value
	Before	After		
WIFAS	66.79±28.28	97.79±56.59	24	0.009
Non-WIFAS	66.92±36.15	108.89±55.75	28	0.000
All groups	66.87±32.44	103.77±55.87	52	0.000

*WIFAS = Weekly Iron Folic Acid Supplementation

Table 7. Serum Ferritin levels before and after product administration in the WIFAS and Non-WIFAS groups.

Groups	Variable		N	P-value
	Before	After		
WIFAS	28.06±23.7	29.05±21.3	24	0.64
Non-WIFAS	13.29±9.5	17.48±12.18	28	0.000
All groups	20.11±18.86	22.82±17.82	52	0.014

*WIFAS = Weekly Iron Folic Acid Supplementation

Table 8. HB levels before and after biopeptide/product administration in the WIFAS and Non-WIFAS groups

Groups	Variable		N	P-value
	Before	After		
WIFAS	12.39±1.33	12.22±1.30	24	0.099
Non-WIFAS	12.06±1.26	11.90±1.33	28	0.088
All Groups	12.21±1.29	12.05±1.31	52	0.016

*WIFAS = Weekly Iron Folic Acid Supplementation

Table 9. Ferritin serum levels before and after biopeptide/ product administration in the normal HB group and Hb levels <12

Groups	Variable		N	P-value
	Before	After		
Hb levels normal	27.34±19.9	30.05±17.84	33	0.109
Hb levels < 12	7.55±6.38	10.27±8.46	19	0.002

4. Discussion

As explained in the product description, in addition to biopeptides, each product sachet (10 g) contains 4.3 g of iron, it can meet 30% of the daily iron needs in the group of adolescents aged 13-18 years according to the regulations of the minister of health of the Republic of Indonesia (Kementerian Kesehatan RI, 2019). Consumption of the test product for 14 days can increase the iron intake of young women who are iron deficient in their bodies. This is shown by the results of research that there was a significant increase in serum ferritin and serum iron after the consumption of the product. Increased levels of iron stored in the body can be detected by increasing serum ferritin levels. The provision of iron supplements is one of the recommended ways to reduce the incidence of anaemia and meet adolescents' iron requirements (Mulugeta *et al.,* 2015; Center for Public Health Innovation, 2017). The result found that there was a significant increase in serum iron after the consumption of the product

The results of the study also showed that those who had low serum ferritrin levels were able to significantly increase their serum ferritrin levels after 14 days of administration of the test product compared to those who had moderate/high serum ferritrin levels. This is in accordance with the results reported by Andrews (2010) and Ganz (2013) that there is a perfect regulation of iron absorption in the intestines to prevent iron deficiency and prevent iron overload, where excess iron in the body is toxic. Iron absorption is modulated by the circulating hormone hepcidin, which inactivates the iron transporter ferroportin. Absorption is also regulated in the intestinal epithelium, through the production of the iron-sequestering protein H-ferritin. A similar result was reported by Braunstein (2018), as stores decrease, the absorption of iron in food increases as compensation. Frazer and Anderson (2017) reported on the regulation of cellular iron homeostasis, cellular iron homeostasis is tightly regulated to maximize the supply of iron when cells are iron deficient and to limit iron supply and promote storage when cells are full of iron. This result supports the results of studies where there is an increase in iron absorption in respondents with low iron status.

Iron intake will increase the body's serum ferritin level and continue to normal and will not increase again. This is consistent with the results of this study that the increase in serum ferritin levels in the group with low iron status indicates the role of the product in increasing iron stores. On the other hand, in the group with good iron status, there was no increase in serum ferritin levels. Hemoglobin status in both groups was normal, this supports an increase in serum ferritin levels when an adequate iron-containing product is administered. As reported by Dignass *et al*. (2018) that serum ferritin is a reserve of iron in the body, if iron levels are sufficient, serum ferritin levels will not increase. Another study showed that standard treatment of iron deficiency anemia in adolescents did not lead to an increase in serum ferritin until hemoglobin levels normalized (Miniero *et al*., 2018).

The results of the study also showed that those who had low serum ferritrin levels were able to significantly increase their serum ferritrin levels after 14 days of administration of the test product compared to those who had moderate/high serum ferritrin levels. This is in accordance with the research by Andrews (2010) and

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The significantly increased absorption of serum iron and serum ferritin in the group with low iron status after consuming the product for 2 weeks compared to the initial iron measurement may be accelerated by the presence of biopeptides in the product. The main components of the product are soybean hydrolysate and seaweed. As reported in the previous paper soybean hydrolysate contains biopeptides which are processed from soy hydrolysis using physical and enzymatic processes to produce fragments of protein with molecular weights less than 15 kd (Laily *et al*., 2014). The ability of protein hydrolysates to chelate is a key factor in promoting iron absorption. Biopeptides could increase the bioavailability of minerals. The size of the amino acids, the amino acid sequence, and the presence of specific amino acids affect the chelating ability and iron bioavailability (Li *et al*., 2017). In a previous paper it has been reported both *in vitro* and *in vivo* that biopeptides from soybean hydrolyzate used in this study have a positive effect on iron absorption (Wijayanti *et al*., 2019; Susanti *et al*., 2020). The mechanism by which protein hydrolysates increase in iron absorption is by keeping the iron dissolved, reducing ferric ions to ferrous, and increasing iron transport through the cell membrane in the gastrointestinal tract (Li *et al*., 2017). This finding was also reported by Andrews (2010) that protein hydrolysate could promote non-haem iron absorption by increasing the concentration of soluble iron to promote the entrance of iron into enterocytes through the DMT1 receptor. It is known that the main source of iron consumed by respondents in this study was non-haem iron. This supports the benefits of the biopeptides used in this study to have a positive role in improving iron status.

Although the biopeptides in this study could significantly increase the serum iron and serum ferritrin of respondents, there was no significant change in hemoglobin levels. The respondent's initial hemoglobin level was normal (≥12g/dl). Administration of the test product during this study could guarantee the iron intake of respondents and could maintain normal hemoglobin levels in both groups. Thus, consumption of the test sample continuously in the group without the addition of supplements (Non-WIFAS) was sufficient to meet the required iron intake.

5. Conclusion

The product formula containing soy biopeptides in this study was proven to have health benefits in increasing serum iron, serum ferritin in respondents with low iron status and maintaining normal hemoglobin levels. However, further testing of these products is still needed to obtain wider scientific evidence so that these products can be used more widely in helping to overcome iron deficiency which has a negative impact on health.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

The authors would like to convey gratitude to all the research participants, female adolescents in Pandeglang, the schools, the Puskesmas, GAIN, and the Ministry of Health that supported the research. The researchers received funding for the research and publication from Badan Pengkajian dan Penerapan Teknologi (BPPT), Badan Riset dan Inovasi Nasional (BRIN), Lembaga Pengelola Dana Pendidikan (LPDP) Ministry of Finance, Indonesia.

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