BIODIVERSITAS
Volume 21, Number 5, May 2020
Pages: 2289-2296

ISSN: 1412-033X
E-ISSN: 2085-4722
DOI: 10.13057/biodiv/d210560

Effectiveness of anemia herbal formula containing *Curcuma zanthorrhiza*, *Elephantopus scaber* and *Amaranthus tricolor* in iron deficiency anemia patients

ULFA FITRIANI♥, ZURAIDA ZULKARNAIN, FAJAR NOVIANTO, ENGGAR WIJAYANTI, AGUS TRIYONO

Medicinal Plant and Traditional Medicine Research and Development Center. Jl. Raya Lawu 11, Tawangmangu, Karanganyar 57792, Central Java, Indonesia. Tel./fax.:+62-271-697010, ♥email: drulfa05@gmail.com

Manuscript received: 4 January 2020. Revision accepted: 29 April 2020.

Abstract. *Fitriani U, Zulkarnain Z, Novianto F, Wijaya E, Triyono A. 2020. Effectiveness of anemia herbal formula containing* Curcuma zanthorrhiza, *Elephantopus scaber, and* Amaranthus tricolor *in iron deficiency anemia patients. Biodiversitas 21: 2289-2296.* Anemia becomes one of the major health problems. Iron supplements often cause discomfort in the digestive tract and it had been related to low compliance. Further research is needed on herbal formulas that have the potential to be complementary or alternative therapies for iron deficiency anemia which is safe and not interfere with digestive tract. This study aimed to evaluate the effectiveness of anemia herbal formula containing *Curcuma zanthorrhiza* Roxb., *Elephantopus scaber*, and *Amaranthus tricolor* compared with iron supplement in Iron Deficiency Anemia (IDA) participants. A total of 128 participants with IDA were recruited and randomly assigned into anemia herbal formula (AH) (n=64) and iron supplement (IS) (n=64). Outcome measures were assessed 4 weeks after intervention. The outcomes of this study were hemoglobin (Hb), mean corpuscular volume (MCV), serum iron (SI), total iron binding capacity (TIBC), and quality of life (QOL) by using short form-36 (SF-36). After 28 days of intervention, there was an increase of Hb, MCV, SI values, and SF-36 scores and a decrease of TIBC values in both groups. Significant differences were found in the mean of Hb, MCV, and SI ($p<0,05$), the higher values were found in IS group. Significant difference also occurred in the mean of TIBC, the SI group had lower value than AH group. In contrast, no significant difference in the mean of quality of life scores between two groups. Anemia herbal formula proved to be an effective complementary therapy by improving QOL in IDA patients.

Keywords: *Amaranthus tricolor*, *Curcuma zanthorrhiza*, *Elephantopus scaber*, iron deficiency anemia

Abbreviations: IDA: Iron Deficiency Anemia, AH: Anemia Herbal formula, IS: Iron supplement, Hb: hemoglobin, MCV: mean corpuscular volume, SI: serum iron, TIBC: total iron banding capacity, QOL: quality of life, SF-36: short form-36

INTRODUCTION

Anemia becomes one of major public health problems worldwide that affects 1,62 billion people in both developed and developing states including Indonesia (Alzaheb and Al-amer 2017)(Petry et al. 2016)(Sumarlan et al. 2018)(World Health Organization 2008). Based on National Research of Health, the proportion of pregnant women suffer from anemia in 2013 was 37,1% and 48,9% in 2018 (National Institute of Health Research and Development 2018).

There are multiple factors that may cause anemia, however, deficiency of iron is the most common one (Al-alimi et al. 2018). Iron deficiency occurs when there inadequate iron intake and absorption (Saha et al. 2018). Iron is critical for the growth of human body cells (Kumari et al. 2017). The absorption of intestinal iron is regulated by several regulatory mechanisms, including dietary, storage, and erythropoietic. These mechanisms control the expression of hepcidin, a key peptide in iron homeostasis. When the loss of iron from the body exceeds its ability, a negative iron balance ensues and eventually affects erythropoiesis causing iron deficiency anemia (IDA) (Liu and Kaffes 2012).

Ferrous sulfate was effective for raising plasma hemoglobin concentration of IDA, however, the long-term consumption caused certain effects, mainly on the gastrointestinal system including nausea, flatulence, abdominal pain, and constipation (PAPDI 2005). Meanwhile, Center for Data and Information, Ministry of Health of the Republic of Indonesia in 2014, revealed that the result of national iron supplementation program was 85% of 95% target (Center for Data and Information 2016). Ethnomedicine study reported that 41 medicinal plants have been used by Indonesian traditional healers for anemia treatment (Badan Litbang Kesehatan 2017).

Temulawak (*Curcuma zanthorrhiza*) has been reported as traditional medicine for anemia treatment (Subositi and Wahyono 2019). The rhizomes of *C. zanthorrhiza* contains two characteristic constituents, those are curcuminoids and volatile oil. Curcuminoids are a mixture of dicinnamoylmethane derivatives such as curcumin, monodemethoxycurcumin and bisdemethoxycurcumin and phenolic and non-phenolic diarylheptanoids. Volatile oil, composed mainly of sesquiterpenes (e.g. β-curcumene, ar-curcumene), xanthorrizol (44.5%), and a small amount of

camphor (Galen and Kroes 2014). Previous studies showed that xanthorrizol has antimicrobial, anti-inflammatory, antioxidant, antihyperglycemic, antihypertensive, antiplatelet, nephroprotective, hepatoprotective, estrogenic, and antiestrogenic properties (Oon et al. 2015). *Amaranthus tricolor* L. reported to have pharmacological activities: hepatoprotective, hematological, hypoglycemic, hypolipidemic, antioxidant activity, antinociceptive, and anti-inflammatory (Srivastava 2017). According to (Rumimper et al. 2014), redleaf amaranth decoction plays a role in elevating hemoglobin levels on Wistar rats. A study conducted by (Aldi et al. 2019) showed that the extract of tapak liman (*Elephantopus scaber* L.) leaves could increase hematopoietic activities (erythrocyte count, reticulocyte count, hemoglobin level, and hematocrit values) The previous study by (Mana et al. 2017) showed that anemia herbs formula consisting of 5 g of *Amaranthus tricolor* leaves, 10 g of *Elephantopus scaber* herbs and 15 g of *Curcuma zanthorrhiza* rhizomes increase of Hb values significantly on thirty-five anemia patients at *Saintifikasi Jamu* Clinic. The mean of Hb values before and after intervention was 9,78 g/dL and 11,09 g/dL. Although this study result has not shown normal values of Hb, it is interesting to be further investigated in the RCT open-label research model whether the anemia herbs formula is able to be an alternative therapy or only complementary in the treatment of IDA.,

Iron supplements often cause discomfort in the digestive tract and it had been related to low compliance (Tolkien et al. 2015). Further research is needed on herbal formulas that have the potential to be complementary or alternative therapies for iron deficiency anemia which is safe and not interfere with digestive tract. The study aimed to evaluate the effectiveness of anemia herbal formula containing *C. zanthorrhiza*, *E. scaber*, and *A. tricolor* compared with iron supplement in IDA study participants.

MATERIALS AND METHODS

Study population

Design study

This study was conducted in Hortus Medicus Clinics (Clinics of Evidence-Based Jamu Development), Medicinal Plant and Traditional Medicine Research and Development Center (B2P2TOOT), Indonesia Ministry of Health at Tawangmangu, Central Java, Indonesia. It involved formal health care facilities (hospital Public Health Center and private practitioners) in some provinces of Indonesia, as well, including Jakarta, West Java, Central Java, Yogyakarta, East Java, Bali, South Sumatra, East Kalimantan, South Sulawesi, and North Sulawesi. Forty-five physicians who had been trained about Evidence-Based Jamu Development (*Saintifikasi Jamu*) were involved in the study. The study design was purposive randomized open-label. The investigators were blinded to intervention allocation.

Participants

Tables of minimum size by Lameshow was used to set sample size (Lwanga and Lemeshow 2006). Saifudin (2002) study assessed the effect of ferrous sulfate given. Results showed that, after 1 month follow up, the number of Hb values 1 g % increasing is 75% Therefore, to get the level of confidence 80% of Hb increasing by Herbs for 1 month in 50% study participants on the significance 5% so Po=0.75 and Pa=0.50. The number of samples based on the table is 58 study participants, with number of lost of follow 10% (based on the previous research), so the final number of participants was calculated as 64 study participants each group. The total of study participants who met the inclusion and exclusion criteria were 128 study participants. They were randomly divided into two groups which are anemia herbs (AH) group (n=64) and iron supplement (IS) group (n=64). Demographic and medical data were obtained from the medical records and interviews conducted in a preliminary study. The inclusion criteria were as follows: men or women patients, aged 18-60 years old, diagnosis by physicians as IDA (Hb 7-10 g/dL, Mean Corpuscular Volume (MCV) <80 fl, serum iron (SI) < 50 mg/dL, Transferrin Iron Binding Capacity (TIBC) > 350 mg dL and signed informed consent form. The exclusion criteria were as follows: Severe anemia (Hb <7 g/dL), anemia not caused by iron deficiency, patients with cancer, heart failure, chronic renal disease, allergy to drugs, and pregnant patient.

Ethics approval

This study was approved by the Ethical Committee of National Institute of Health Research and Development (NIHRD) (No.LB.02.01/2/KE.249/2018) and written informed consent was obtained from all participating study participants.

Procedures

Preparation of materials

Curcuma zanthorrhiza, *Elephantopus scaber*, and *Amaranthus tricolor* were collected from March to April 2018 from areas around Karangpandan and Tawangmangu, Karanganyar, Central Java, Indonesia. The plants were identified by botanist at the Medicinal Plant and Traditional Medicine Research and Development Center, Karanganyar, Central Java, Indonesia. The voucher specimens were deposited in the herbarium department.

In anemia herbs group, each study participant was given herbal formula which consisted of dried simplicia of *C. zanthorrhiza* 15 g, *E. scaber* 10 g, and *A. tricolor* 5 g. Before being administered to the study participant, the simplicia was managed and controlled by Post Harvest Division, B2P2TOOT Tawangmangu, Central Java, Indonesia. The formula was prepared by boiling 1 L of water, then put the ingredients in boiling water for 15 minutes. Study participants were instructed to drink the filtered water twice a day after breakfast and dinner for 4 weeks.

In control group, the subject consumed iron supplement "HF". HF was purchased from PT Gratia Husada Farma, Indonesia. The composition of Hufabion was ferrous

fumarate 250 mg, manganese sulfate 0.2 mg, copper sulfate 0.2 mg, vitamin C 50 mg, folate acid 1 mg, and cyanocobalamin 10 mcg.

Measures

All study participants were screened regarding inclusion criteria. The Hb, MCV, SI, and TIBC of all eligible subjects were measured in one reference laboratory. According to the results of the laboratory tests, 128 study participants were included in the study. All laboratory tests were repeated at 2 and 4 weeks of intervention.

Intervention

258 men and women were screened regarding inclusion criteria recruited for this study. Participants were asked to take their AH two times daily after breakfast and dinner for 4 weeks and HF one time daily after breakfast or dinner for 4 weeks. Every participant had weekly controlled regarding correct consumption of AH or hufabion and evaluated the clinical symptoms, as well.

Outcome measurements

Baseline measurement of Hb and MCV was carried out in 2 and 4 weeks, while SI, TIBC, and SF-36 were in 4 weeks.

SF-36

SF-36 is an instrument for various conditions as well as the general population and very popular instrument for evaluating health-related Quality of Life (QOL) (Lins and Carvalho 2016). There are thirty-six items assess patient health across 8 domains including bodily pain (BP), general health perceptions (GH), mental health (MH), physical functioning (PF), role limitations due to emotional health problems (RE), role limitations due to physical health problems (RP), social functioning (SF), and vitality (VT). All items use categorical response options. From the individual subscales, 2 component summary scores are generated for physical and mental health. The physical component score (PCS) consists of PF, RP, BP, GH, VT, and the mental component score (MCS) consist of GH, VT, SF, RE, MH; the GH and VT subscales overlap between the 2 overall components. The scores for each subscale are converted to norm-based scores, with a mean of 50 and a standard deviation of 10. A score of 100 represents the best health. The validity and reliability of the SF-36 have been well established (Strauss et al. 2016).

Data analysis

All data were analyzed by SPSS version 24. Independent t-test and chi-square test were conducted to compare the demographic characteristics. Continuous data (Hb, MCV, SI, TIBC, SF 36) were screened for normality. The paired t-test to see the difference before and after treatment within each group and independent t-test to see the difference between two groups. The Mann Whitney test was used where there is an abnormal data distribution on Kolmogorov-Smirnov test result.

RESULTS AND DISCUSSION

Results

A total of 128 study participants were randomly assigned after being considered eligible by the physicians (Figure 1). There is no difference in baseline groups. In the end, 128 study participants were analyzed. None of the study participants dropped out of the study. The study participants were recalled 1 time per week. At baseline, there was no significant difference ($p>0.05$) in demographic characteristics such as gender, age, occupation, and body mass index (BMI) between Anemia herbs (AH) and iron supplement (IS) group (Table 1).

After 4 weeks of intervention, there were significant differences ($p<0.05$) of the outcome parameter in both anemia herbs and iron supplement groups. the value of Hb, MCV also SI increased and TIBC was decreased significantly in all study participants who received iron supplements. The AH group showed the increased mean Hb, MCV, SI, and decreased TIBC not significantly. There was significant difference ($p<0.05$) in the value of Hb, MCV, Si, and TIBC between anemia herbs and iron supplement groups. In the SF 36 parameters, there was no significant difference ($p>0.05$) between anemia herbs and iron supplement groups. The score of SF 36 was increased significantly in all study participants who received anemia herbs and also iron supplement (Table 2).

The mean score of each domain of SF 36 as shown in Table 3. In the AH and IS groups, the mean score of each domain SF 36 was consistently increased after 4 weeks intervention (Figures 2 and 3). In the AH group, the increase of score of GH domain was highest among the other domains, while the score of RP domain was lowest among the other domains. In the IS group, the increase of score of BP domain was highest among the other domains and the score of RP domain was lowest among the other domains.

We also analyze each domain of SF 36 between AH and IS groups. There are no significant differences between two groups were observed in the 4th week regarding domain of SF-36 (Table 3).

Discussion

This study involved physicians of *Saintifikasi Jamu* who were scattered in almost all regions of Indonesia. In our knowledge, this study is the first open-label RCT to explore the effectiveness of herbs containing *Curcuma zanthorrhiza*, *Elephantopus scaber*, and *Amaranthus tricolor* compared with iron supplement. Mana et al.'s research in 2017 on the same herbal formula was a single-arm study without control. The results of both studies showed an increase in Hb levels at the end of the intervention. However, the increase in this study was not significant when compared to the baseline, while Mana et al.'s result were significant. There were different characteristics of the subjects. Ardiyanto's has smaller and homogenous subjects since only took place at RRJ (Mana et al. 2017).

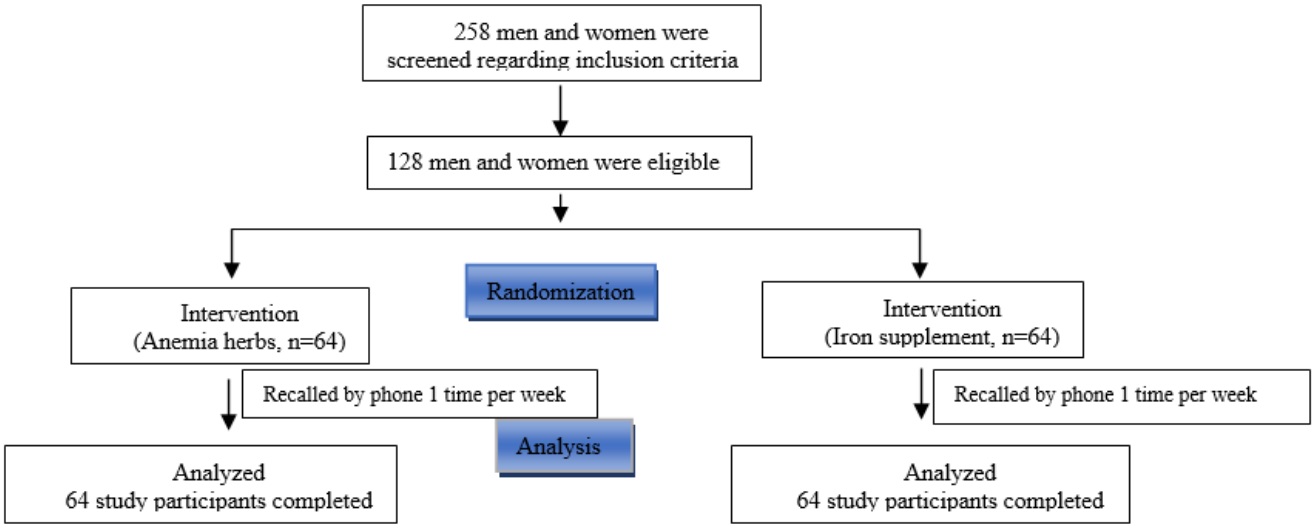

Figure 1. Diagram showing patient flow

Table 1. Baseline characteristics of the study population

Variable	AH group	IS group	P-value
Gender			0,465*
Male	3 (4.7%)	4 (6.3%)	
Female	61 (95.3%)	60 (93.8%)	
Age	37.39±10.79	34.63±13.25	0.198**
Occupation			0.087*
Housewife	15 (23.4%)	15 (23.4%)	
Private employee	18 (28.1%)	17 (26.6%)	
Farmer	4 (6.3%)	1 (1.6%)	
Government officer	15 (23.4%)	18 (28.1%)	
Student	2 (3.1%)	8 (12.5%)	
Enterpreneur	10 (15.6%)	5 (7.8%)	
BMI			0.900*
Underweight	9 (14.1%)	9 (14.1%)	
Normal	29 (45.3%)	34 (53.1%)	
At-risk of obesity	14 (21.9%)	11 (17.2%)	
Obese I	10 (15.6%)	9 (14.1%)	
Obese II	2 (3.1%)	1 (1.6%)	

Note: *p<0.05 significantly differences of chi square, **p<0.05 significantly differences of independent t-test

Table 2. The outcome parameter of AH and IS groups before and after intervention

Variables	AH (n=64)			IS (n=64)			P-value between groups
	Baseline Mean ± SD	4 weeks Mean ± SD	Mean difference	Baseline Mean ± SD	4 weeks Mean ± SD	Mean difference	
Hb	10.19 ± 1.44	10.35 ± 1.39	+0.16	10.83 ± 8.65	12.59 ± 12.18	+1.76[a]	0.001*
MCV	74.09 ± 9.11	74.51 ± 9.52	+0.42	72.76 ± 9.16	77.48 ± 7.31	+4.72[a]	0.050**
SI	41.53 ± 38.77	41.75 ± 43.79	+0.22	29.57 ± 21.80	82.77 ± 75.45	+53.2[a]	0.000*
TIBC	372.32 ± 68.75	366.73 ± 67.05	-5.59	354.84 ± 89.19	322.34 ± 94.31	-32.5[a]	0.000*
SF 36	81.13 ± 10.25	84.74 ± 7.94	+3.61[a]	81.19 ± 14.23	85.62 ± 10.05	+4.43[a]	0.323*

Note: [a] Significant difference within group (p < 0.05), *p<0.05 significantly differences of Mann whitney, **p<0.05 significantly differences of independent t-test

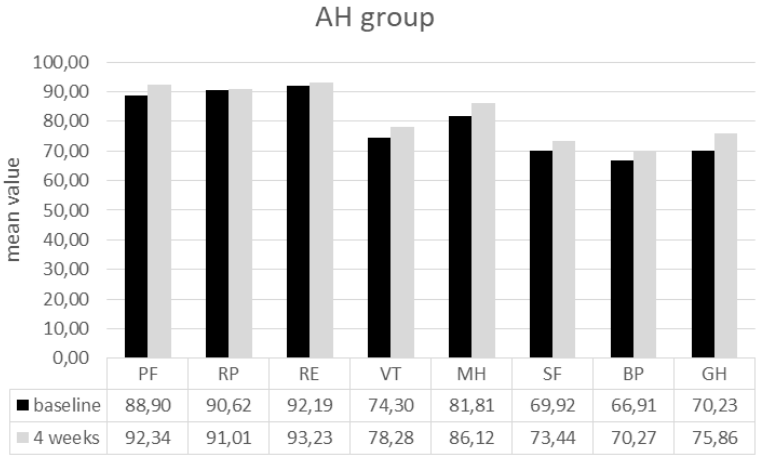

Figure 2. The mean score of each domain of SF 36 in AH group

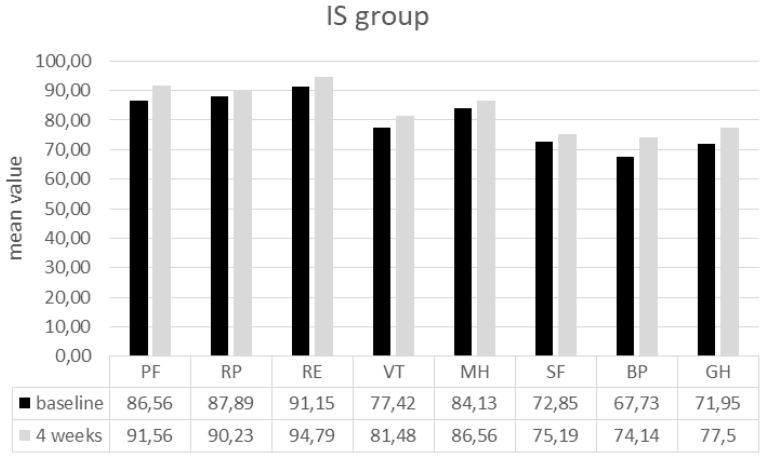

Figure 3. The mean score of each domain of SF 36 in IS group

Table 3. Domain of SF-36 between AH and IS groups

	P* value							
	PF	**RP**	**RE**	**VT**	**MH**	**SF**	**BP**	**GH**
Baseline	0.550	0.729	0.888	0.118	0.240	0.304	0.877	0.349
4 weeks	0.718	0.309	0.230	0.140	0.386	0.547	0.307	0.321

Note: *p<0.05 significantly differences of Mann Whitney

The sociodemographic data showed that the most of study participants are women aged under 40 years. About 28.1% of the study participants on the iron supplementation group are government officer and 28.1% of the study participants on the anemia herbs group are private employee. The study about body mass index (BMI) showed that majority of the study participants are normoweight. It is consistent with other previous studies about prevalence of anemia among women in Turkey revealed that most of women diagnosed with anemia, 34.4% were on reproductive age (Saydam et al. 2017). The study carried out by (Ugwuja et al. 2015) reported that the occupation and body mass index (BMI) had no effect of anemia prevalence. According to literature gender, age and gastrointestinal diseases were risk factors for IDA. Women at reproductive age have higher prevalence because of loss blood regularly from menstruation (Levi et al. 2019).

The characteristic of herbal medicine that gave to the participants about are the number of component formulas, each component has spesific functions in order to produce an synergistic effect (Chan et al. 2011). The ingredients that compose the formula are *Curcuma zanthorrhiza*, *Elephantopus scaber*, and *Amaranthus tricolor*. Study about *Amaranthus tricolo*r reported that iron content of this

plant was 3.9 mg/100 g (Yudhistira et al. 2017), whereas the review study by (Topwal 2019) reported that the amaranth leaves consist of 2.3-3.2/100 g of fresh leaves. The study about *E.scaber* showed that this plant presence of minerals especially iron, calcium, magnesium, and zinc (Kabeer and Prathapan 2014) (Santhosh Kumar et al. 2012). The other study revealed that the iron content on *Elephantopus scaber* were 45.4% (Djati et al. 2017). One of bioactive compound of *Curcuma zanthorrhiza* was curcumin. Other previous study showed that curcumin decreased hepcidin (Laviolle et al. 2017), that was known as the main regulator in iron metabolism (Purwanto 2012). The anemia herb was aimed to increase the the value of Hb, MCV, SI, and decrease the value of TIBC. It might also enhance healthy longevity, as well. It was expected that the AH would improve the overall outcome parameter for IDA patients. However, current study showed no overall improvement in outcome parameters. The outcome parameters of this study consist of the Hb, MCV, SI, TIBC and SF-36.

This study revealed that AH might have a limitation in term of capability for increasing Hb, MCV, and SI value into the normal range. Previous study reported that anemia herbs consist of *Curcuma zanthorrhiza*, *Elephantopus scaber*, and *Amaranthus tricolor* can increase the value of Hb significanty on the IDA study participants in Hortus Medicus Clinic (Mana et al. 2017). A number of possible explanations of the findings need to be considered. One potentially important factor is the bias of this study that did not examine the helminthic infection. The World Health Organization (WHO 2002) currently recommends the use of the Kato-Katz method, direct smear microscopy formol-ether concentration (FEC), McMaster, FLOTAC and Mini-FLOTAC to detect the human soil-transmitted helminth (STH). All of these methods rely on visual examination of a small sample of stool (Nikolay et al. 2014). Although this study did not use gold standard for detection the helminthic infection, the study participants were asked if they had history of helminthic infection. Helminthic infection is one of factors that contributed to IDA. The mechanism of helminthic infections causes IDA by reducing nutrient intake and interfering iron metabolism and transport direct or indirectly (Adebara et al. 2011).

Another potential explanation for the findings in the current study is the relatively short treatment. The 4 weeks intervention time was determined based on the previous study by Mana et al. (2017) and follow thebrenchmark for succesful treatment of IDA 2g/dL Hb increase in 3 weeks (Schrier 2015). However, the results of this study showed no significant improvement Four weeks might not enough to evaluate the effect of anemia herbs. According to Motoo et al (2005), twenty three patients were randomized into two groups of placebo and 9 g Ninjinyoeito (NYT), a herbal medicine formula per day for 24 weeks. The result showed that anemia was significantly reduced in the NYT group compared with the control group. Another study about effect of herbs to their efficacy showed that effective treatment after 8 weeks intervention (Nisa and Astana 2019).

Although AH cannot increase the value of Hb, MCV, SI into the normal range, but this study demonstrated that AH increased QOL by using SF-36's score the IDA patients as same as IS treatment. AH can increase the QOL of the IDA study participants significantly after 28 days intervention. When it is compared to the inter group, the domain of SF-36 were shown to be not significant difference ($p>0.005$). In the AH group, the highest increase of SF 36's domain is the general health perceptions. Otherwise, the highest increase of SF 36's domain in the IS group is the bodily pain domain. *Curcuma zanthorrhiza* contains curcumin that can protect and improved liver function (Pramono et al. 2018). The liver has regulatory functions in iron homeostasis (Yiannikourides and Latunde-dada 2019). This can be related to the increased of general health perceptions in AH groups. Findings of the bodily pain becomes the domain with the highest score increase in IS group is in line with previous study. Study conducted by (Okam et al. 2017)showed that treatment with iron supplementation resulted significant increases in all domain of the SF 36 except role limitations due to emotional health problems (RE) domain.

The interest in the concept of QOL is relativey recent in health (Nurhayati and Widowati 2016). One of the QOL instruments administered in this study was a multidimensional generic SF-36 measure, which is sensitive for treatments. Non-treated anemia can decrease the quality of life that that can increase the morbidity (Sihombing et al. 2017). In Japan, the quality of life of the IDA patients is low, although most were asymptomatic (Ando et al. 2006). Sinergism effect of *Curcuma zanthorrhiza*, *Elephantopus scaber*, and *Amaranthus tricolor* can increase QOL in the IDA study participants. A recent systematic review of 10 RCT studies indicated that herbal medicines can be effective in improving the quality of life in menopause women (Mirzaei Najmabadi et al. 2017). Patient with the other chronic disease like hypertension who had pharmaceutical and herbal medicine had more risk to be good QOL (Nurhayati and Widowati 2016).

This study was the first open label and randomized controlled trial in Indonesia. Contrary to our expectations, there were no significant Hb, MCV and SI increasing after four weeks of anemia herbs intervention. More importantly, Anemia herbs is still valuable for improvement of QOL score among patients with IDA, compared to these conventional therapies.

ACKNOWLEDGEMENTS

We would like to thank Medicinal Plant and Traditional Medicine Research and Development Center, National Institute of Health Research and Development (NIHRD), Indonesian Ministry of Health, Indonesia, for their support in doing this study. We also thank P.R. Widhi Astana and Fanie Indrian M for excellent technical assistance.

REFERENCES

Adebara VO, Ernest SK, Ojuawo AI. 2011. Association between intestinal helminthiasis and serum ferritin levels among school children. Open J Pediatrics 1: 12-16. DOI: 10.4236/ojped.

Al-alimi AA, Bashanfer S, Morish MA. 2018. Prevalence of iron deficiency anemia among university students in Hodeida Province, Yemen. Anemia 2018: 4157876. DOI: 10.1155/2018/4157876.

Aldi Y, Dillasamola D, Rifa N. 2019. Effect of ethanol from extract of tapak liman leaves (*Elephantopus scaber* Linn.) on hematopoiesis of anemia mice. Intl J Pharm Res Allied Sci 8 (2): 157-167.

Alzaheb RA, Al-amer O. 2017. The prevalence of iron deficiency anemia and its associated risk factors among a sample of female University Students in Tabuk, Saudi Arabia. Clinical Medicine Insights: Women's Health 10. DOI: 10.1177/1179562X17745088.

Ando K, Morita S, Higashi T, Fukuhara S, Watanabe S, Park J, Kikuchi M, Kawano K, Wasada I, Hotta T. 2006. Health-related quality of life among Japanese women with iron deficiency anemia. Qual Life Res 15 (10): 1559-1563. DOI: 10.1007/s11136-006-0030-z.

Badan Litbang Kesehatan, Kementrian Kesehatan RI. 2017. Eksplorasi Pengetahuan Lokal Etnomedisin. Badan Litbang Kesehatan, Kementrian Kesehatan RI, Jakarta. [Indonesian]

Center for Data and Information, Ministry of Health. 2016. Situasi Gizi Di Indonesia. Jakarta. [Indonesian]

Chan KKL, Yao TJ, Jones B, Zhao JF, Ma FK, Leung CY, Lau SK, Yip MW, NganHYS. 2011. The use of chinese herbal medicine to improve quality of life in women undergoing chemotherapy for ovarian cancer: a double-blind placebo- controlled randomized trial with immunolog. Ann Oncol 22 (10): 2241-2249. DOI: 10.1093/annonc/mdq749.

Djati SM, Rahma YA, Dwijayanti DZ, Rifai M, Rahayu S. 2017. Synergistic effect of *Elephantopus scaber* L and *Sauropus androgynus* L Merr extracts in modulating prolactin hormone and erythropoiesis in pregnant typhoid mice. Tropic J Pharm Res 16: 1789-1795.

Galen Van E, Kroes B. 2014. Assessment report on *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich) rhizoma. European Medicines Agency, London.

Kabeer AF, Prathapan R. 2014. Phytopharmacological profile of *Elephantopus scaber*. Pharmacologia 5: 272-285.

Kumari R, Bharti RK, Singh K, Sinha A. 2017. Prevalence of iron deficiency and iron deficiency anaemia in adolescent girls in a tertiary care hospital. J Clin Diagn Res 11 (8): 10-12. DOI: 10.7860/JCDR/2017/26163.10325.

Laviolle B, Rennes CHU, Rennes CHU. 2017. Curcuma decreases serum hepcidin levels in healthy volunteers: a placebo-controlled, randomized, double-blind, cross-over study. Fundam Clin Pharm 3 (5): 567-573. DOI: 10.1111/ijlh.12426.

Levi M, Simonetti M, Marconi E, Brignoli O, Cancian M, Masotti A, Pegoraro V, Heiman F, Cricelli C, Lapi F. 2019. Gender differences in determinants of iron-deficiency anemia : a population-based study conducted in four european countries. Ann Hematol 98 (7): 1573-1582. DOI: 10.1007/s00277-019-03707-w.

Lins L, Fernando Martins Carvalho. 2016. SF-36 total score as a single measure of health-related quality of life : scoping review. SAGE Open Medicine 4. DOI: 10.1177/2050312116671725.

Liu K, Kaffes AJ. 2012. Iron deficiency anaemia : a review of diagnosis, investigation and management. Eur J Gastroenterol Hepatol 24: 109-16. DOI: 10.1097/MEG.0b013e32834f3140.

Lwanga L. 2006. Sample Size Determination in Health Studies. World Health Organization, Geneva.

Mana TA, Ardiyanto D, Saryanto,. 2017. Peningkatan nilai hemoglobin, mcv, mch dan feritin pada kasus anemia defisiensi besi dengan ramuan jamu di Klinik Saintifikasi Jamu Hortus Medicus. Media Gizi Mikro Indonesia 8 (2): 127-136. DOI: 10.22435/mgmi.v8i2.604 [Indonesian]

Najmabadi M, Khadijeh, Mahdavian M, Hosseinzade H, Makvandi S, Leyla K. 2017. Herbal medicines for improving quality of life in menopause women : a systematic review. Women's Health & Gynecology 3 (2). www.scientonline.org.

National Institute of Health Research and Development, Ministry of Health. 2018. National Research of Health. Jakarta. [Indonesian]

Nikolay B, Brooker SJ, Pullan RL. 2014. Sensitivity of diagnostic tests for human soil-transmitted helminth infections : a meta-analysis in the absence of a true gold standard. Intl J Parasitol 44 (11): 765-774. DOI: 10.1016/j.ijpara.2014.05.009.

Nisa U, Astana PRW. 2019. Evaluation of antiurolithic herbal formula for urolithiasis : a randomized open label clinical study. Asian J Pharm Clin Res 12 (4): 88-93. DOI: 10.22159/ajpcr.2019.v12i4.30232.

Nurhayati, Widowati L. 2016. Herbal therapy and quality of life in hypertension patients at health facilities providing complementary therapy. Health Sci J Indon 7: 32-36.

Okam MM, Koch TA, Tran M. 2017. Iron supplementation, response in iron-deficiency anemia : analysis of five trials. Am J Med 130 (8): 991.e1-991.e8. DOI: 10.1016/j.amjmed.2017.03.045.

Oon FS, Nallappan M, Tee TT, Shohaimi S, Kassim NK. 2015. Xanthorrhizol : a review of its pharmacological activities and anticancer properties. Cancer Cell Intl 15: 100. DOI: 10.1186/s12935-015-0255-4.

PAPDI. 2005. Anemia Defisiensi Besi. PB PAPDI, Jakarta. [Indonesian]

Petry N, Olofin I, Hurrell RF, Boy E, Wirth JP, Moursi M, Angel MD, Rohner F. 2016. The proportion of anemia associated with iron deficiency in low, medium, and high human development index countries : a systematic analysis of national surveys. Nutrients 8: 693. DOI: 10.3390/nu8110693.

Pramono S, Arifah FH, Nugroho AE. 2018. Hepatoprotective activity of *Curcuma xanthorrhiza* Roxb. on paracetamol- induced liver damage in rats and correlation with their chemical compounds. Thai J Pharm Sci 16: 28705-28745.

Purwanto DS. 2012. Peran hepsidin sebagai regulator metabolisme besi. Jurnal Biomedik 4: 88-95. [Indonesian]

Rumimper AE, Posangi J, Wuisan J. 2014. Uji efek perasan daun bayam merah (*Amaranthus tricolor*) terhadap kadar hemoglobin pada tikus wistar (*Rattus norvegicus*). Jurnal E-Biomedik 2: 4. DOI: 10.35790/ebm.2.2.2014.5519.

Saha U, Dharwadkar PS, Sur S, Vishaharini V, Malleshappa M. 2018. Plant extracts as an astounding remedy to anemia - a review. Ann Plant Sci 4: 2166-2171.

Saifudin AB. 2002. Buku Panduan Praktis Pelayanan Kesehatan Maternal dan Neonatal. Yayasan Bina Pustaka Sarwono Prawirohardjo, Jakarta. [Indonesian]

Santhosh Kumar S, Subramanian A, Uma C, Rengaiyan R, Sambandan K, Sekar KG, Sudarshan M, Chakraborty A. 2012. Trace elemental analysis and antimicrobial activities of *Elephantopus scaber* L. J Phytology 4 (4): 8-13.

Saydam KB, Sarac F, Genc RE, Turfan EC. 2017. Prevalence of anemia and related factors among women in Turkey. Pak J Med Sci 33 (2): 433-438.

Schrier SL. 2015. So you know how to treat iron deficiency anemia. Blood 126 (17): 1971. DOI: 10.1182/blood-2015-09-666511.

Sihombing J, Hakim L, Andayani TM, Irijanto F. 2017. Quality of life of chronic kidney disease patients with routine hemodialysis in general hospitals in Sleman Yogyakarta. Intl J Pharm Pharm Sci 9 (2): 213-216.

Srivastava R. 2017. An updated review on phyto-pharmacological and pharmacognostical profile of amaranthus tricolor : a herb of nutraceutical potentials. Pharma Innov J 6 (6): 124-129.

Strauss WE, Dahl V, Vadhan-raj S, Bernard K, Dickerhoof R, Li Z, Lee F. 2016. Effects of IV iron treatment with ferumoxytol on health-related quality of life of patients with iron deficiency anemia. J Commun Support Oncol 14: 342-50. DOI: 10.12788/jcso.0232.342.

Subositi D, Wahyono S. 2019. Study of the Genus *Curcuma* in Indonesia used as traditional herbal medicines. Biodiversitas 20 (5): 1356-1361. DOI: 10.13057/biodiv/d200527.

Sumarlan ES, Windiastuti E, Gunardi H. 2018. Iron status, prevalence and risk factors of iron deficiency anemia among 12- to 15-year-old adolescent girls from different socioeconomic status in Indonesia. Makara J. Health Res 22 (1): 46-52. DOI: 10.7454/msk.v22i1.8078.

Tolkien Z, Stecher L, Mander AP, Pereira DIA. 2015. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta- analysis. Plos One 10 (2): e0117383. DOI: 10.1371/journal.pone.0117383.

Topwal M. 2019. "A review on amaranth : nutraceutical and virtual plant for providing food security and nutrients." Acta Scientific Agriculture 3 (1): 9-15.

Ugwuja EI, Ogbonnaya LU, Obuna AJ, Awelegbe F, Uro-chukwu H. 2015. Anaemia in relation to Body Mass Index (BMI) and socio-demographic characteristics in adult Nigerians in Ebonyi State. J Clin Diagn Res 9 (1): 7-10. DOI: 10.7860/JCDR/2015/9811.5485.

WHO. 2008. Worldwide Prevalence of Anaemia 1993-2005. World Health Organization, Geneva.

Yiannikourides A, Latunde-dada GO. 2019. A short review of iron metabolism and pathophysiology of iron disorders. Medicines (Basel) 6 (3): E85. DOI: 10.3390/medicines6030085.

Yudhistira B, Affandi DR, Nusantari PN. 2017. Effect of green spinach (*Amaranthus tricolor* L.) and tomato (*Solanum lycopersicum*) addition in physical, chemical, and sensory properties of marshmallow as an alternative prevention of iron deficiency anemia effect of green spinach (*Amaranthus tricolor*). IOP Conf Ser Earth Environ Ser 102 (1): 012007. DOI: 10.1088/1755-1315/102/1/012007.