Moringa oleifera leaf powder supplementation improved the maternal health and birth weight: a randomised controlled trial in pregnant women

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Abstract

Background This study was carried out to assess the effects of *Moringa oleifera* leaf powder (MOLP) on maternal health and birth weight.

Method Subjects were anaemic pregnant women at third trimester living in a rural area of South Sulawesi Province, parity one to three and singleton pregnancy. They were randomly assigned into two groups (each n=19); daily MOLP distributed into four capsules (each 500mg), or iron-folic acid (IFA), containing 60mg iron and 400mcg folic acid. The intervention was for 2 months. Measurements included anthropometric, haemoglobin, perceived stress, cortisol and birth weight.

Result Most of the participants were between 20–35 years old (74%) and had low economic status (92.1%). At baseline, all variables were similar in both groups, except for perceived stress and cortisol which were higher in the MOLP group. Haemoglobin improved significantly in MOLP and IFA groups, but the amount of improvement was higher in the MOLP group (1.46±0.35 vs. 0.76±0.42). Perceived stress decreased significantly in the MOLP group after treatment (16.16±8.10 to 9.68±3.82) but did not change in the IFA group (11.16±4.41 to 13.11±5.42). Cortisol level declined in the MOLP group after treatment (22.46±3.96 to 19.55±4.17) but increased significantly in the IFA group (18.53±3.66 to 22.13±5.68). Mean birth weight was significantly higher in the MOLP group (3390g±383 vs. 2937g±400).

Conclusion Giving 2g of MOLP per day for 2 months during the third trimester of pregnancy is effective to improve the health status indicators of pregnant women and to increase infant birth weight in the moderately anaemic pregnant women.

Introduction

Multiple micronutrient (MMN) deficiencies during pregnancy are widespread in many low- and middle-income countries. Several micronutrients including iron, calcium, vitamin A, B-complex, D, E and zinc are commonly consumed in less than adequate quantities by pregnant mothers due to economic constraints and other cultural and geographical influences.[1,2] These deficiencies, together with low body mass index, contribute partly to maternal mortality, low birth weight, still birth, and neonatal or perinatal mortality.[3] Therefore, a MMN supplementation has been recommended as an important nutrition program during pregnancy.

Several reviews have been carried out to assess the evidence on the effects of MMN supplementation on maternal health, birth outcomes, and biological mechanisms.[4–7] Ramakrishnan et al.[7] found that prenatal maternal MMN resulted in a reduction in the incidence of birth weight and small-for-gestational age (SGA) infants. In addition, a review of 17 studies using MMN supplementation[8] indicated that, although there were no significant benefits on maternal anaemia, MMN supplementation showed benefits for reducing SGA than iron-folic acid (IFA) supplementation. Thus, replacing IFA supplementation with MMN supplementation was recommended, particularly in developing countries.[8] However, the implementation of MMN supplementation is difficult in countries with low–middle incomes due to limited resources.

Moringa oleifera (MO) is currently emerging as a potential resource for MMNs. MO leaves contain a range of nutrients as well as bioactive compounds.[9–11] It has more vitamin A than carrots, and more calcium than milk. MO also has a higher amount of iron, compared to spinach, as well as containing more vitamin C than oranges. Moreover, MO is also rich in potassium and phytochemical agents, i.e. phenolic acid and flavonoids.[12,13] MO leaves have been used in some developing countries to combat malnutrition problems in both mothers and children.[14–17] It appears to be a safe supplement, with no adverse effects reported in human studies, though standardisation and validation of the product remains an issue,[18] and human clinical trials using a standardised dose of both extract and powder are still limited.

In the last 5 years, we have demonstrated that the MO leaf ethanol-extract could improve maternal nutrition status, haemoglobin[15,19,20] and reduce stress.[21] Ishak et al.[19] found that 1g of MO leaf ethanol-extract together with IFA supplement improved haemoglobin, compared to those who received only IFA supplement. In addition, Nadimin et al.[20] compared non-anaemic pregnant mothers receiving 2g of MO leaf ethanol extract with non-anaemic pregnant mothers receiving a conventional dose of IFA. They showed significant improvement of haemoglobin in both groups. This study suggested that MO leaf extract could replace IFA supplementation during pregnancy in an undernourished population. Moreover, a comparison study between MO leaf extract and powder[22] suggested that MO leaf powder (MOLP) should be considered as a supplement in the future because it is simple to produce, readily available, and could be independently produced in communities.

Phytochemical compounds in MOLP provide another possible benefit to pregnant mothers. Prenatal maternal stress is associated with poor pregnancy outcomes, including maternal salivary cortisol concentration with low infant birth weight and duration of gestation.[23,24] Our previous studies provide evidence that MO leaf extract reduced stress during pregnancy and biomarkers of oxidative stress (*malondialdehyde* and *8-hydroxy-2'-deoxygenosine*).[20,21,25] Therefore, there are several reasons to consider MO as a promising local resource for achieving improved maternal health and pregnancy outcomes to babies.

Our previous study showed that MOLP at a dose of 1g per day significantly increased birth weight[26,27] compared to IFA supplementation alone; however, it did not improve haemoglobin concentration. Therefore, an additional dosage may be needed to improve haemoglobin, especially for anaemic pregnant mothers. This study was carried out to determine the effect of MOLP (2g/day) on haemoglobin, stress, cortisol and birth weight among moderately anaemic pregnant mothers in the third trimester of pregnancy compared to IFA supplementation alone. We hypothesised that pregnant mothers who received 2g of MOLP daily for 2 months would have an improved haemoglobin, decreased stress and cortisol, and higher birth weight, compared to those who received IFA.

Methods

Study setting

The study was conducted in Jeneponto District, which is approximately 150km from Makassar, the capital of South Sulawesi Province, Indonesia. Jeneponto has an area of 750km^2 and is occupied by 330,735 people. A survey in 2013 showed that maternal malnutrition and low birth weight babies are prevalent in Jeneponto. Jeneponto has 11 sub-districts and 13 primary healthcare centres (called Puskesmas). Puskesmas Tamalatea was chosen for this study. All pregnant mothers at the beginning of the third trimester of pregnancy who registered in Puskesmas Tamalatea from January 2018 were the target population of the study.

Source of *Moringa oleifera* leaves

MO leaves were taken from two different areas in South Sulawesi Province, Jeneponto and Soppeng District, due to the limitations of obtaining raw material (fresh MO leaves) in one area only. All of the leaves were grown by the villagers in both areas. Although from different sources, all of the processes were carried out exactly the same. Firstly, MO leaves were washed and then dried by using a drying medium that has been made locally (avoiding sunlight). After perfectly drying, the leaves were crushed in a blender until powdered consistency. The MOLP was put into the capsule without any additional compounds.

Trial design

This randomised control trial (RCT) included participants randomly allocated into one of two groups.

The eligibility criteria were the age of pregnancy 29–31 weeks, having haemoglobin level 10–11g/dl, parity one to three, and singleton pregnancy. Those who were eligible (n=40) were randomly allocated into two groups. A randomisation sequence was generated by hand and allocation to each group performed by the field investigators, with mothers asked to take a small paper with letter A or B from a can. If the mother took the paper with letter A, she received capsules from bottle A and vice versa. The treatment assigned to letters A and B was known only by the principal investigators (VH). Mothers were given a bottle containing 28 capsules, coded A or B according to the letter she took at the randomised stage.

The study commenced in January 2018 when all pregnant women in the third trimester who came to the Puskesmas were screened for eligibility in the study (Figure 1). Four of the field investigators (YN, HS, RAH and MR) screened 102 mothers; 40 were eligible for participation and consented to participate in the study. Written informed concerned was received from each mother. During the intervention, two subjects dropped out. The first was due to family issues and the other refused to consume the capsules. Therefore, the total subjects in this study were 38; 19 in the MOLP group and 19 in the IFA group. Data for these subjects were included in an intention to treat (ITT) analyses.

There were two interventions in the study, MOLP and IFA. Both interventions were put in similar capsules with capacity of 500mg each. IFA was a tablet obtained from the conventional nationwide program. Each tablet contained 60mg elemental iron and 400mcg folic acid. In order to create the same appearance for the trial, each IFA tablet was mixed with amylum to 2g and put evenly into four capsules.

Mothers were instructed to take two capsules in the morning and two capsules in the afternoon/night during 2 months of intervention period. Thus, each mother in one group received four capsules each containing 500mg of MOLP every day (2g in today per day), while in the other group each mother received four capsules containing 60mg elemental iron and 400mcg folic acid every day.

At the end of each week, compliance with the intervention was assessed by field investigators through capsule counts. The number of consumed capsules and the reason of mothers' rejection were written on a standard form. The field investigator sent short electronic messages to the mothers each morning and afternoon to remind mothers to take the capsules. Mothers were asked to answer the messages otherwise the field workers would give a call to encourage consumption of the capsules. All mothers included in the analyses consumed all capsules (100%).

Outcome variables and measurement

The primary outcome variables, measured before and after the intervention, were haemoglobin, perceived stress,

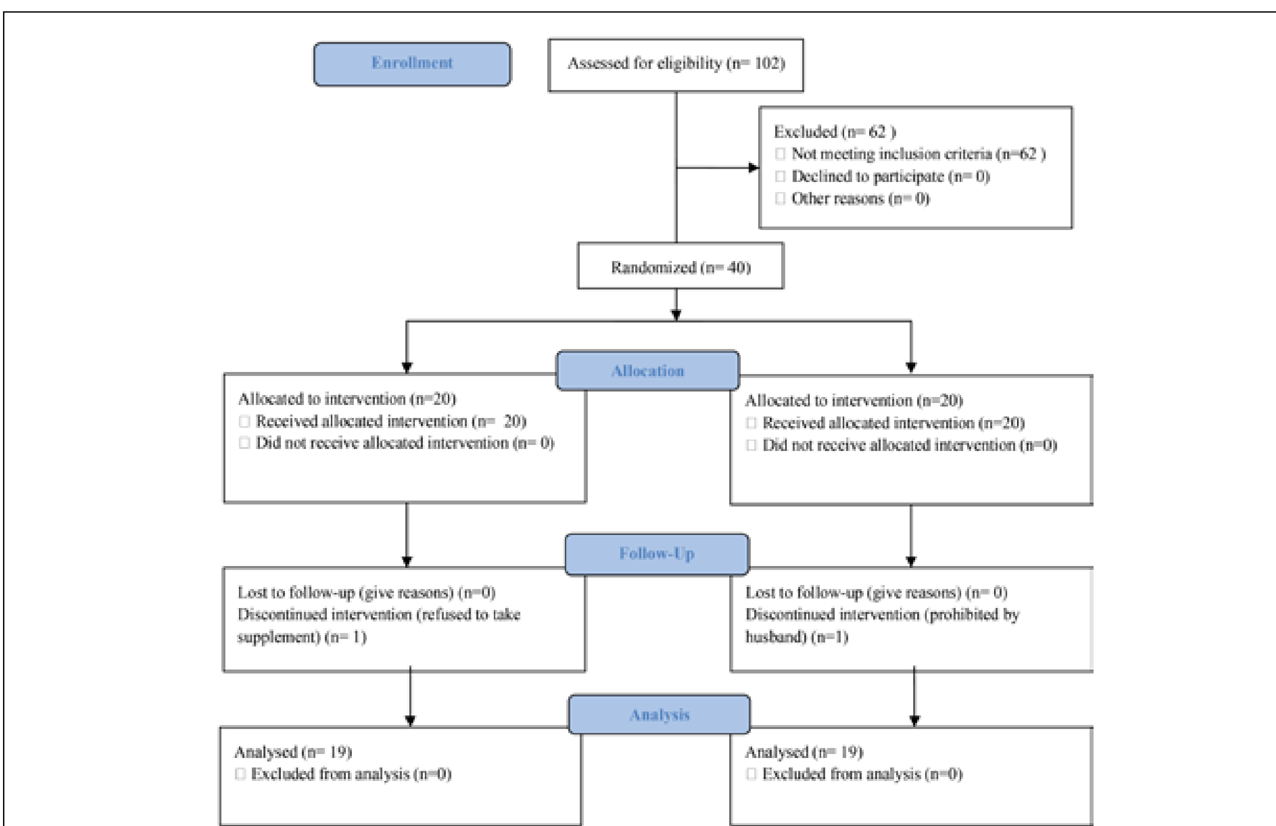


Figure 1. Flow diagram of the study participants

and salivary cortisol concentration. Secondary outcome were infant birth weight, measured after birth. All measurements were performed by the field investigators. The characteristics of mothers were assessed at baseline using a standard questionnaire. These were related to the family's socio-economic status, including education and occupation of mother and father, family's income per month, number of family members, and family support for the current pregnancy.

Haemoglobin was measured using a haemoglobin analyser (DiaSpect®, EKF Diagnostic, UK). A microcuvette was used to a finger prick of capillary blood samples. The blood sample was inserted into the device and the result was shown on the screen. Haemoglobin level was measured in the morning around 10am. Anaemia was defined as haemoglobin level below 11gr/dl.

Perceived stress was measured using the DASS 42 (Depression Anxiety Stress Scale)[28,29]. This standardised questionnaire contains 42 questions with a 5-point scale for each answer (value 0–4). The stress assessment was interpreted from questions 1, 6, 8,11, 12, 14, 18, 22, 27, 29, 32, 33, 35 and 39. The total score was categorised into normal (score 0–14), mild (score 15–18), moderate (score 19–25), severe (score 26–33), and very severe (score >33). The tool has been translated into different languages and used in several developing countries, including in the Indonesian setting[30].

Salivary cortisol concentration was measured by using a Salivary Cortisol ELISA Kit (Diagnostics Biochem, Canada). Mothers were given a cup to collect 2ml of their saliva in the morning before having breakfast. Afterward, the field investigators collected the cups and brought them to a specific room before transporting the cups to the laboratory at Hasanuddin University, Makassar. According to the standard, the normal value of cortisol using saliva in the morning is 5–21.6µg/dl.

Birth weight was measured by midwives an hour after the delivery by using an infant weight scale. Each village has one midwife, and mothers were asked to contact the midwife when they had signs for giving a birth. The infant is considered low birth weight if the newborn weighed less than 2,500g.

Sample size calculation

The sample size was calculated using a formula for hypothesis tests for a population mean with a two-side test[31]. Based on the previous study[26], the difference of birth weight between two groups (MOLP and IFA) was 350g with standard deviation of 450g. A sample size of 40 was needed to detect difference between groups with 90% power and 10% no response with a 95% confidence level.

Statistical analyses

The data was entered, cleaned and analysed using SPSS statistical software version 25. Descriptive analyses were first performed for the main variables. Comparisons between the groups at baseline were assessed using Chi-square test for categorical variables, and independent t-test for continuous variables. The changes within each group (before and after intervention) were analysed using paired t-test while the differences between groups were analysed using independent t-test. A General Linear Model was used to perform an ANOVA to assess the difference in birth weight after adjusting for perceived stress and cortisol variables as covariates[32]. The two variables were put as covariates since they were found to be significantly different between groups at baseline.

Results

Socio-demographic characteristics

The characteristics of subjects were similar in both groups (Table 1). Most of the participating mothers were aged 20–35 years old (73.7%), and around half of them were primiparas (55.3%). One-third of the participants were low-educated, in which most of them were graduated from primary school or less (34.2%), and almost all of them had low economic status (92.1%). In addition, almost all mothers were housewives (92.1%) and had adequate family support for their pregnancy (92.1%).

At baseline, there were six mothers (15.8%) suffering from mild stress, 10 mothers (26.3%) suffering from moderate to severe stress, and it was higher in the MOLP group than the IFA group (57.9% vs. 26.3%, respectively MOLP and IFA groups, p=0.041). Similarly, high cortisol level was found in 16 mothers (42.1%) and was higher in the MOLP group than the IFA group although the difference was not statistically significant (57.9% vs. 26.3% respectively for MOLP and IFA groups, p=0.052).

Effects of intervention

Before the intervention, the characteristics of both groups were comparable, except for perceived stress. It showed that perceived stress was significantly higher in the MO group compared to the IFA group (Table 2). After the intervention, although there were no significant differences between groups for the mean haemoglobin level, the increment of haemoglobin over time was significantly higher in the MOLP group compared to the IFA group (1.48±0.35 vs. 0.77±0.42, p=0.001). The improvement for the MOLP group was 0.71g/dl or 92% higher than the IFA group. Perceived stress reduced significantly in the MOLP group but did not change in the IFA group and the change in stress was significantly different between the two groups (-6.46±4.24 vs. 1.95±1.00, p=0.008). Besides, salivary cortisol concentration reduced significantly in the MOLP group but increased significantly in IFA group. The changes in cortisol was significantly different between the two groups (-2.91±7.20 vs. 3.60±6.37, p=0.005).

Figure 2 presents the effect of the intervention on the prevalence of anaemia and perceived stress. Anaemia prevalence declined to zero in the MOLP group, while the anaemia prevalence in the IFA group reduced to 47.30%. The difference of anaemia prevalence after intervention between groups was significant (x^2=11.79, df=1, p=0.001). The participants perceived stress (mild to severe) at baseline was higher in the MOLP group than the IFA group (57.90% vs. 21.10%, x^2=3.89, df=1, p=0.049). After 8 weeks treatment, perceived stress was significantly higher in the IFA group, compared to the MOLP group (63.2% to 26.3%, respectively for IFA and MOLP groups; x^2=6.91, df=1, p=0.009).

Figure 3 shows a box plot of birth weights in the MOLP and IFA groups. The median birth weight in the MOLP group was higher than the IFA group. The comparison of means between groups using ANOVA test showed a significantly higher mean in the MOLP group both before and after adjusting for stress and cortisol level at baseline (p<0.05). This study also showed that only one infant was found with low birth weight, and it was found in the IFA group (5.3%). Additionally, more newborns in the MOLP group weighed more than 3,000g (84.2% vs. 57.9%, respectively for MOLP and IF groups, x^2=3.99, df=2, p=0.074, data is not shown). Moreover, 10 mothers (52.6%) in the MOLP group and four mothers in the IFA group (21.1%) had birth weight 3,500g or above.

Discussion

We found that giving a supplement of MOLP for 8 weeks to moderately anaemic pregnant mothers in the last trimester significantly improved the haemoglobin levels as well as reduced perceived stress and cortisol compared to IFA supplements. The prevalence of anaemia also reduced to zero among pregnant mothers receiving MOLP. In addition, birth weight was higher in mothers who received MOLP compared to those receiving IFA. To our knowledge, this is the first study examining the effect of MOLP against IFA supplementation in pregnant mothers on maternal health together with birth weight.

The change on the anaemia in this study is different from other studies comparing MMN against IFA

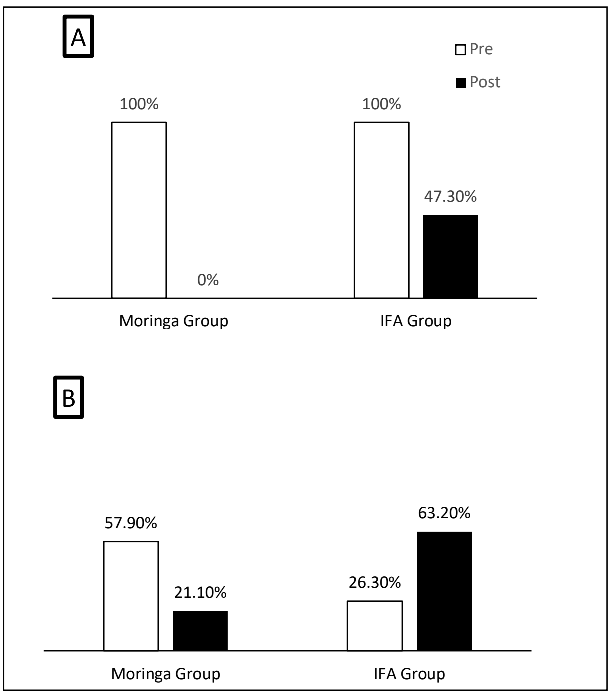
Table 1. The characteristics of subjects at baseline

Variable	Moringa oleifera (MOLP) group (n=19)		Iron-folic acid (IFA) group (n=19)		Total (n=38)		p-value
	n	%	n	%	n	%	
Mother age							
• <20	2	10.5	2	10.5	4	10.5	1.000
• 20-35	14	73.7	14	73.7	28	73.7	
• >35	3	15.8	3	15.8	6	15.8	
Parity							
• Primigravida	11	57.9	10	52.6	21	55.3	0.744
• Multigravida	8	42.1	9	47.4	17	44.7	
Age of pregnancy							
• 29 weeks	7	36.8	4	21.1	11	28.9	0.549
• 30 weeks	10	52.6	12	63.2	22	57.9	
• 31 weeks	2	10.5	3	15.8	5	13.2	
Education							
• Unfinished primary	3	15.8	1	5.3	4	10.5	0.677
• Primary school	4	21.1	5	26.3	9	23.7	
• Junior high school	7	36.8	6	31.6	13	34.2	
• Senior high school	5	26.3	7	36.8	12	31.6	
Economy status							
• Moderate	1	5.3	2	10.5	3	7.9	0.547
• Low	18	94.7	17	89.5	35	92.1	
Family support							
• Adequate	18	94.7	17	89.5	35	92.1	0.547
• Less	1	5.3	2	10.5	3	7.9	
Height							
• <160cm	11	57.9	14	73.7	25	65.8	0.305
• >=160cm	8	42.1	5	26.3	13	34.2	
Stress*							
• Normal	8	42.1	14	73.7	22	57.9	0.041
• Mild	4	21.1	2	10.5	6	15.8	
• Moderate – severe	7	36.8	3	15.8	10	26.3	
Cortisol**							
• Normal	8	42.1	14	73.7	22	57.9	0.052
• High	11	57.9	5	26.3	16	42.1	

*Stress was categorised according number of score; normal (1–14), Mild (15–18), Mod-severe (>=19)

**Cortisol was categorised normal (<21.6ug/dl), high (>=21.6ug/dl).

supplementation among pregnant mothers in several countries.[8,33] Haider et al.[8] reviewed 16 randomised intervention studies that compared MMN and IFA in pregnant mothers. They found that MMN supplementation did not change the anaemia prevalence compared to IFA (RR=1.03; CI: 0.87–1.22). Similarly, a review from 14 studies comparing MMN and iron with or without folic acid by Allen et al. from the United Nation International Multiple Micronutrient Preparation (UNIMMAP)[33] showed that there was no difference on haemoglobin between MMN and iron supplementation with or without folic acid. This study, however, supports the previous study in India[34] and Senegal[14] that MOLP improved haemoglobin.



prevalence of pregnant mothers, before and after the intervention. After the intervention, the difference between groups for anaemia was significant (x^2=11.79, df=1. p=0.001). The prevalence of stress was high in the MOLP group at baseline (x^2=3.89, df=1. p=0.049) but was high in the IFA group after intervention (x^2=6.91, df=1. p=0.009)

Interestingly, the present study used only 2g of powder. The studies in India by Kushwaha et al.[34] provided 7g of MOLP daily for 3 months in postmenopausal women, and the haemoglobin level increased 17.5%. On the other hand, Idohou-Dossou et al.[14] provided Senegalese lactating women with 100g of MOLP per week for 3 months, and the haemoglobin level increased 3.8%. We found that the improvement of haemoglobin level in this study was adequate (14.3%) after 2 months of intervention. Since the daily consumption of MOLP is uncommon in Indonesia (mostly MO was boiled or mixed with other leafy vegetables), putting the powder in the capsule was more acceptable as a supplement to combat malnutrition. Compared to our previous study in a similar population[27], in which 1g of MOLP supplementation among pregnant mothers for 3 months period did not improve haemoglobin, we observe that 2g of MOLP is adequate in combating anaemic or iron deficiency problems in moderately anaemic pregnant mothers.

Iron is not the only nutrient in MO that could contribute to the improvements observed in this study. MO leaf is a good source of amino acids, vitamins, minerals and various phytochemical agents.[9,10,35,36] The amount of iron in MO leaf is also high relative to other plants. On the other hand, vitamin A and C are micronutrients that enhance the iron absorption. Therefore, the combination of minerals, vitamins, and other bioactive compounds in MO appear to be synergistic in their effects on iron absorption and metabolism. A study by Saini et al.[37] showed that the iron bioavailability of MO leaf is better than the bioavailability of elemental iron supplements in rats. Consequently, our study contributes to the evidence that MO should be considered an edible plant that can be the basis of effective interventions for treatment of anaemia in women who are pregnant.

It is interesting to note that MOLP reduced stress and cortisol level in the pregnant mothers of our study. This supports our previous study carried out with a MO leaf extract in pregnant mothers employed as informal workers in urban areas[21]. The reduction of stress and cortisol level is potentially associated with the antioxidant activities in MOLP. MO has approximately 46 antioxidants and is a powerful source of natural antioxidants.[36,38–40] The major antioxidants in MO are quercetin, kaempferol, beta-

Table 2. Effects of the intervention on maternal health

Variable	Pre*	Post	P-values	Change	P-values
Haemoglobin (g/dl)					
• MOLP group (n=19)	10.22±0.21	11.68±0.40	0.001	1.46±0.39	0.001
• IFA group (n=19	10.20±0.20	10.95±0.38	0.001	0.76±0.39	
Stress (score)					
• MOLP group (n=19)	16.16±8.10	9.68±3.86	0.017	-6.47±10.70	0.008
• IFA group (n=19	11.16±4.41	13.11±5.42	0.278.	1.95±7.59	
Cortisol level (ug/dl)					
• MOLP group (n=19)	22.46±3.96	19.55±4.17	0.095	-2.91±7.20	0.005
• IFA group (n=19	18.53±3.66	22.13±5.69	0.024	3.60±6.37	

*Differences between groups at baseline for haemoglobin (p=0.692), stress (p=0.024), and cortisol (p=0.003).

sitosterol, caffeoylquinic acid and zeatin. In addition, MO leaf has micronutrients with antioxidant activity or directly linked to antioxidant processes: selenium and zinc. This study showed that the MOLP has a similar potential as the MO leaf extract in reducing stress and its consequences.

We found that birth weight in mothers who received MOLP is 353g higher than their counterpart in the IFA group. This study is consistent with and perhaps more beneficial than trials conducted using MMN. A cluster randomised double-blind controlled trial conducted in China by Lingxia Zeng et al.[41] found that birth weight was 42g (95% confidence interval 7–78g) higher in the MMN group compared with the folic acid group. Moreover, a meta analyses from 12 trials of MMN supplementation compared with IFA revealed a small increase of birth weight 7.6g (95% confidence interval 1.9–13.3g) and 10% reduction in low birth weight.[42] The significant increase of birth weight in the MOLP group may be related to several possibilities, consistent with the effects discussed above for maternal health. Firstly, MOLP improves iron metabolism (measured from the haemoglobin level) with associated effects on birth weight.[43,44] Secondly, MOLP provides other micronutrients, as well as other bioactive compounds that improve iron absorption as well as having independent effects on maternal health and infant outcomes, as shown with MMN supplementation. Lastly, the high content of antioxidants in MOLP reduces stress and its effects on birth weight.[23]

However, the study has some limitations. Importantly, we could not standardise the composition of MO leaves used in this study. It is realised that the mineral composition (such as calcium, copper, iodine, iron, magnesium, selenium and zinc) is influenced by the environment and soil composition,[12] and growing conditions will influence other components. Nonetheless, we have established that MOLP is as effective as leaf extract in its effects on maternal health and pregnancy outcomes. In addition, subjects in this study were moderately anaemic pregnant mothers during the third semester of pregnancy. More studies among non-anaemic pregnant mothers before pregnancy or during early pregnancy are needed to better understand the potential of MO in combating MMN deficiencies.

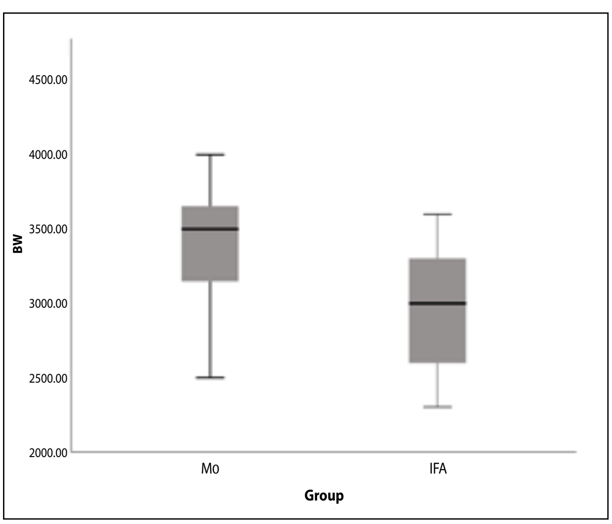


Figure 3. Birth weight (BW) in the MOLP and IFA groups. The mean of birth weight was higher in MOLP group (3390±383g vs. 2937±400g, p=0.004). After correction for stress and cortisol at baseline, the adjusted mean was higher in the MOLP group (3356±409g vs. 3023±409g, p=0.024)

Conclusion

We conclude that giving a supplementation of MOLP for 8 weeks to moderately anaemic pregnant mothers in the last trimester improved significantly the haemoglobin level as well as reduced perceived stress and cortisol. In addition, birth weight was higher in pregnant mothers who received MOLP compared to those received IFA. MO is widely grown in Asia and Africa and has no adverse health effects reported.

Ethics approval

Ethics approval for this study was provided by the Ethics Committee at the School of Medicine, Hasanuddin University, Makassar, Indonesia, number 1116/ H4.8.4.5.31/PP36-KOMETIK/2017 on 29 December 2017. Each mother provided written informed consent during registration of the study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare no conflicts of interest.

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The authors received no funding for this study.

Authors' contributions

VH supervised the study proposal development, data collection and data analyses at the first step. Then further analysed and interpreted the data, and was a major contributor in writing the manuscript. AI was involved in writing the manuscript and the critical revision of the final manuscript. GM reviewed, further analysed and interpreted the data and supervised manuscript development. WN supervised the study proposal development, data collection and data analyses at the first step. YN, HS, RAH, MR developed the study proposal, collected and managed data in the field, and analysed data at the first step. All authors read and approved the final manuscript.

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