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Efficacy of an iron-fortified gummy on iron-deficiency anemia in young women

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ABSTRACT

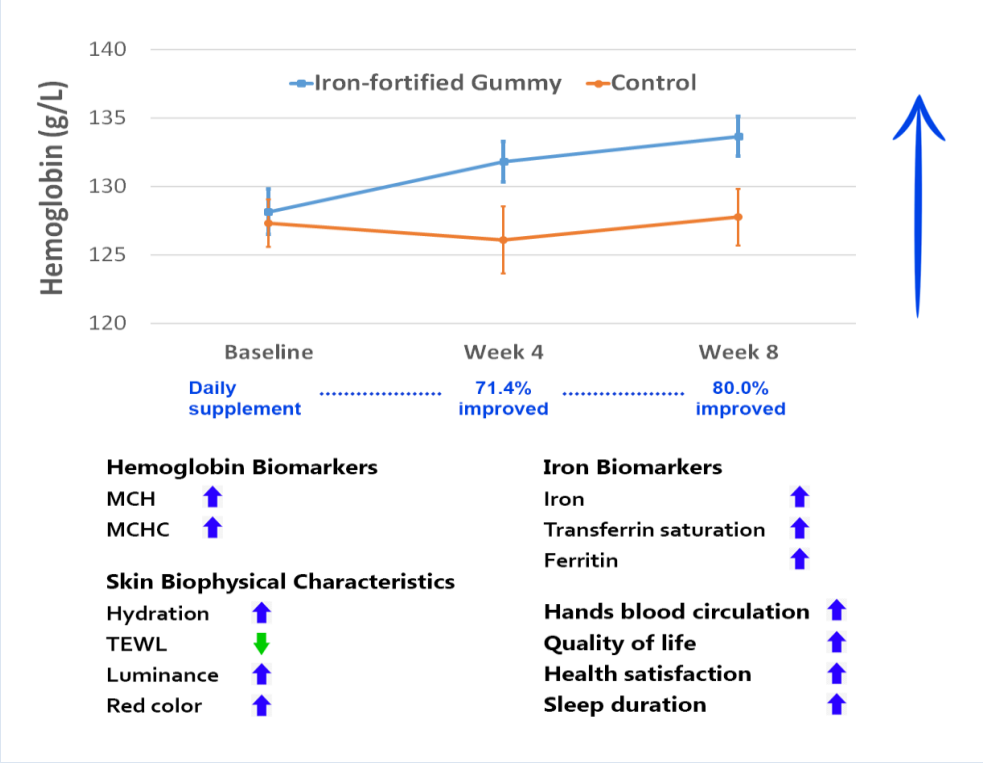
Objective: We conducted this single-center, double-blinded, randomized and placebo-controlled study to explore the efficacy of an iron-fortified gummy on relieving iron-deficiency anemia in young Chinese women. Participants' blood hemoglobin level was set as the primary outcome. The secondary objectives were to assess the effects of the iron-fortified gummy on participants' blood iron levels, skin barrier functions, skin temperature regulating ability, menstruation and leucorrhea status, sleep quality, and overall quality of life.

Methods: Seventy female participants aged 18-35 years with moderate iron-deficiency anemia (blood hemoglobin 90-120 g/L) were recruited and randomly assigned to an intervention group or a placebo group. We supplemented the diets of the participants with an iron-fortified gummy or a placebo for eight weeks. Their blood hemoglobin level, iron biomarkers, skin biophysical characteristics, hand temperature, self-reported menstruation and leucorrhea status, life quality and sleep quality were recorded at baseline, mid-way through the study and the end of the study. We compared the differences of the above outcomes between the intervention group and the control group.

Results: After eight weeks of daily iron-fortified gummy intake, 80% of the participants showed improvement in blood hemoglobin concentration, with a mean increase of 14.5 g/L (95% confidence interval: 9.4, 19.5 g/L) compared to the control. Their serum iron and ferritin levels had significantly increased. They also had improved facial skin hydration and complexions, reduced transepidermal water loss, and accelerated temperature recovery in their hands. Intake of the iron-fortified gummy effectively reduced the incidence of menstrual headaches and insomnia. Participants reported prolonged sleep time, improved energy level, mobility, mental concentration, ability to engage in daily activities and work, as well as better perception of quality of life and health satisfaction.

Conclusion: Daily consumption of the iron-fortified gummy over eight weeks could help build up blood iron levels to generate hemoglobin, relieve iron-deficiency anemia and related symptoms in young Chinese women. Intake of iron through gummy on a daily basis is an effective method to gradually increase the participants' iron levels, leading to sustainable long-term benefits.

Study registration: Chinese Clinical Trial Registry (ChiCTR2200061345).



INTRODUCTION

Iron, as an essential element needed to form hemoglobin, also plays a key role in transporting oxygen through the human body [1]. Iron deficiency (ID) caused by insufficient iron storage in the body is a common clinical condition, which remains the leading cause of anemia [2–4]. According to the health industry standards for anemia screening in China [5] and the World Health Organization (WHO) guidelines [6], blood hemoglobin level is often used as a common indicator for anemia screening: hemoglobin <120 g/L for female or <130 g/L for male can be diagnosed as anemia. The 2020 report on Chinese residents' chronic diseases and nutrition shows that the anemia rate for residents aged 18 years and over in China is 8.7%, and the main affected groups are children, adolescents, and women [7]. According to the WHO reports, about 40% of children under 5 years old and 30% of women from 15 to 49 years of age are affected by anemia in 2019 [8]. In China, the prevalence of anemia among residents aged 18 to 44 years is 10.2%, with 5.8% in males and 15.0% in females [9]. Due to physiological reasons such as menstruation and pregnancy, higher prevalence of anemia is observed in female adults compared to male adults [2,10], especially among women between 18 and 29 years of age [11].

As the predominant nutritional deficiency causing anemia, ID is present even when other causes of anemia are recognized [12]. Except when caused by gastrointestinal bleeding and menstruation in women, iron deficiency anemia (IDA) is often related to insufficient dietary iron intake and absorption [13]. It is noted that iron intake among the majority of healthy women of reproductive age is far below the recommended amount [14]. The current methods applied worldwide to treat IDA are mainly oral iron supplementation, intravenous iron therapy and nutrition interventions [15]. Traditional oral iron supplements are convenient to administer and have good clinical effects, but also have relatively large adverse reactions, while the intravenous iron is effective but inconvenient and expensive [16]. At present, nutritional intervention through iron-fortified foods is the most economical, effective, and feasible method to treat IDA as recognized by the global nutrition community [17]. The main challenge of nutritional intervention is that iron absorption can be affected by potential inhibitors present in commonly fortified foods. Improvement of diet composition and food processing methods can reduce the reaction of the fortification iron with the inhibitors, and thus enhance iron absorption [18].

In this study, we performed an eight-week intervention with an iron-fortified gummy product to evaluate its efficacy among participants with IDA. The gummy contains four iron fortifiers, including sodium ferric ethylenediaminetetraacetate (NaFeEDTA) [19], ferric pyrophosphate (FePP) [20], ferrous bisglycinate [21] and heme iron polypeptide (HIP) [22], all of which have significant effects on treating iron deficiency, reducing the rate of anemia, and are easily absorbed. The primary objective was to assess the effect of the iron-fortified gummy product on improving hemoglobin level in blood. The secondary objectives were to evaluate whether the product would improve the health of the participants with IDA through biomarkers of serum iron level, skin conditions, skin temperature recovery on fingers, and through self-assessments on quality of life, sleep quality, menstruation, and leucorrhea status.

MATERIALS AND METHODS

Study design: This study is a single-center, double-blinded, randomized, placebo-controlled trial. According to the WHO diagnostic criteria for anemia [6], 70 young female participants with IDA were enrolled to ensure at least 60 complete the study, considering a 15% possible dropout rate. They were randomly assigned to an intervention group or a control group, with each group consist of 35 participants. An iron-fortified gummy or a placebo was given to the participants in the corresponding group for daily intake during an eight-week study period. Efficacy assessments of the iron-fortified gummy in relieving anemia and related symptoms were conducted following the study intervention. The study procedures complied with the standards of the Declaration of Helsinki. This study was reviewed and approved by the Institutional Review Board of Shanghai Nutrition Society. All participants were informed about the research and signed the informed consent form before enrollment.

Study product: The iron-fortified gummy product under study was supplied by Hangzhou Minayo Technology Co. Ltd. (Hangzhou, China). It contained 3.3 mg of iron in each 3 g gummy, and each package contained 30 gummies. The placebo was made with maltodextrin with the same weight of 3 g each and 30 counts per package. Both the gummy product and the placebo had the same package and administration instructions. Participants were asked to take two gummies at a time after a meal, and three times a day for a total of eight weeks.

Study subjects: Female participants aged between 18 and 35 years, who were not pregnant and had blood hemoglobin level of 90-120 g/L, were eligible for the study. We excluded participants with the following

conditions: anemia caused by organic diseases; on-going gastrointestinal symptoms treatment; presence of other organic diseases that may affect intestinal function, such as prior gastrointestinal excision, colon or rectal cancer, inflammatory bowel disease, diabetes, hyperthyroidism or hypothyroidism, congenital megacolon, scleroderma or anorexia; being on a diet, doing excessive exercises, taking weight control medications or appetite suppressants in the last three months; being clinically diagnosed with any diseases that may confound the study product effect, including obvious gastrointestinal disorders, liver, kidney, endocrine, blood, respiratory and cardiovascular diseases; current or past abuse of alcohol, drugs or supplements which may cause intestinal dysfunction or affect the product evaluation; current frequent use of drugs that may affect the immune system; use of cathartics or other digestive substances in the past two weeks; use of drugs or nutritional products that contain iron within 10 days before the start of the study; being pregnant or breastfeeding presently, or having childbearing potential during the study.

Participants agreed not to take any drugs, supplements, other iron products, iron-containing medications, or nutritional products, and not to take part in any other interventional research during the study period. Antibiotics use was restricted unless necessary due to medical reasons, in which case the type, dosage and duration of intake were recorded.

Efficacy evaluation: We measured the efficacy outcomes at baseline, week 4 and week 8 of the study. The primary outcome was blood hemoglobin level based on lab tests. A 20 ml whole blood sample was drawn from each participant at each time of measurement to determine blood hemoglobin level, as well as the levels of mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC). Serum iron profile was measured by ferritin concentration, iron concentration, transferrin saturation (TSAT), unsaturated iron binding capacity (UIBC), and total iron binding capacity (TIBC). For safety analysis, serum alanine aminotransaminase (ALT), aspartate aminotransferase (AST) and uric acid levels were also obtained to assess liver and kidney functions. Urine samples were collected at each visit for urine routine tests.

We used non-invasive bioengineering devices to measure stratum corneum hydration (SCH), transepidermal water loss (TEWL), skin complexion and pigmentation on the face. All measurements were performed on both the left and the right side of each participant's cheeks at baseline, week 4 and week 8, using individual probes by the same investigator. The room temperature during the testing period was controlled at 21±1℃. All measurements were repeated three times, and the average of the three readings were used for analyses. Skin SCH was measured using Corneometer CM825 (Courage+Khazaka electronic GmbH, Koln, Germany), and TEWL was measured by AquaFlux AF200 (Biox Systems Ltd., London, England). Skin brightness and redness (hemoglobin content) was assessed by Antera 3D (Miravex Ltd., Dublin Ireland), which measured brightness and erythema values through 3D scan of the skin.

The temperature of the skin on the hand was measured by thermal imaging camera FLIR E76 (Teledyne FLIR LLC, Wilsonville, United States). Participants were requested to soak their hands in 10 °C water for 5 minutes. The thermal imaging camera was used to take photos of hands before water immersion, immediately after immersion, and at 2, 4, 6, 8, and 10 minutes after immersion for temperature measurements. Data were collected on participant's index finger, middle finger and ring finger, and the average temperature of the three fingers was used to analyze the recovery of hand temperature after water immersion.

Participants reported their quality of life, sleep quality and gastrointestinal symptoms via the Chinese

language versions of the World Health Organization Quality of Life-BREF (WHOQOL-BREF) questionnaire and the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire.

The WHOQOL-BREF is an international quality of life assessment instrument. It contains 26 items which measure the broad domains of physical health, psychological health, social relationships, and environment [23]. The raw item scores in the questionnaire range from 1 to 5 and were summarized to four domain scores, plus two independent scores for the overall perception of quality of life and health. These scores were then transferred to a 100-point scale.

The GSRS is a validated gastrointestinal questionnaire that employs a 7-level Likert scale of 15 items, rated based on the intensity and frequency of gastrointestinal symptoms experienced during the previous week [24]. Higher scores indicate more severe symptoms reported by the participants. The combination scores from the GSRS items represent five clusters including abdominal pain, reflux, indigestion, diarrhoea, and constipation [25]. Participants were instructed to report their menstruation and leucorrhea status at each study visit. Length of menstrual cycle and menstrual bleeding, and any abnormal menstrual symptoms were recorded. The volume, color and odor of the leucorrhea were also documented.

Participants recorded the name and number of foods consumed for each meal and snacks during the three days before each study visit. Daily energy and nutrients intake were derived using commercially available software Feihua (Beijing Bowenshixun Technology Ltd., Beijing, China), and the three-day average data were used for food composition analysis.

Physical activities in the one week before each visit were recorded. Participants reported their weekly frequencies and durations of walking, moderate-intensity activities and vigorous-intensity activities. A continuous measure for metabolic equivalent of task (MET) minutes per week was derived for each type of activity following the Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire [26].

Anthropometric measures including weight, height, and body mass index (BMI) were obtained. All participants' demographic information, socioeconomic status, and family medical history were also recorded to assess the randomization process of the study.

Statistical analysis: Demographic and baseline characteristics were summarized. Descriptive statistics of outcomes were provided at baseline, middle of the study (week 4) and end of the study (week 8). Mean and standard deviation (SD) were reported for normal distributed variables, median and quantiles were reported for non-normal continuous variables, and frequency (%) were reported for discrete variables.

The outcomes were tested for distributional assumptions, and transformations or nonparametric tests were used if deemed necessary. The inter-group differences at each visit were tested using one-way analysis of variance (ANOVA) for normal distributed outcomes and Kruskal Wallis test for non-normal or ordinal outcomes. Relative risks of anemia between the two groups at post-intervention visits were calculated. The intra-group changes from baseline were evaluated using paired t-test for normal distributed outcomes and Wilcoxon signed ranks test for non-normal or ordinal outcomes. A mixed model was used to assess the non-invasive instrumental skin measurements, accounted for multiple measurement sites. For discrete outcomes, the inter-group differences were tested by Fisher's exact test; the intra-group differences versus baseline were tested by McNemar test for dichotomous outcomes and by repeated measures logistic regression for multi-level discrete outcomes.

The count and rate of adverse events (AEs) and serious adverse events (SAEs) were summarized. The inter-group difference on the overall rate of AEs was

tested by Fisher's exact test. All enrolled participants who consumed at least one dose of the study products were included in the analyses. Missing data from early withdrew subjects were not replaced or imputed. All statistical tests were performed at a significance level of 0.05. The SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses of this study.

RESULTS

A total of 70 eligible individuals participated in the study and all started product consumption. Among them, three from the iron-fortified gummy group and four from the placebo group withdrew during the study for personal reasons, resulting a 10% overall attrition rate. Of all enrolled participants, the mean age was 31.6 years (SD: 3.9 years) in the iron-fortified gummy group and 31.2 years (SD: 3.4 years) in the placebo group. The two groups were comparable in all baseline characteristics (Table 1). Throughout the study, all participants complied with the restrictions of dietary supplements other than the study products and kept similar diets and physical activity levels (supplementary tables S1 and S2).

Table 1. Baseline characteristics

Variables	Iron-fortified Gummy (n=35)	Placebo (n=35)	p-value
Age	31.6±3.9	31.2±3.4	0.652
Height (cm)	162.2±4.2	163.1±5.1	0.408
Weight (kg)	62.6±11.7	61.5±12.5	0.704
BMI (kg/m²)	23.8±4.5	23.2±5.1	0.585
Number of previous abortion(s) [a]	0 (0, 0)	0 (0, 0)	0.722
Education			0.693
Elementary school or lower	1 (2.9)	1 (2.9)	
High school	7 (20.0)	3 (8.6)	
College	10 (28.6)	13 (37.1)	
Undergraduate	15 (42.9)	17 (48.6)	
Graduate	2 (5.7)	1 (2.9)	
Age of menarche (year)	13.4±1.2	13.7±1.2	0.322
Has given birth	23 (65.7)	25 (71.4)	0.797
Number of previous live birth [a]	1 (0, 1)	1 (0, 1)	0.560
Current smoker	2 (5.71)	1 (2.9)	1.000
Current alcohol drinker	2 (5.71)	3 (8.6)	1.000
Current tea drinker	18 (51.4)	20 (57.1)	0.574
Average sleeping duration (hour/day)	7.1±0.9	7.0±0.9	0.739
Usual time when falling in sleep [a]	23:30 (23:00, 0:00)	23:30 (23:00, 0:00)	0.810

Unless otherwise noted, continuous variables are summarized by mean±standard deviation, and the differences are tested by one-way analysis of variance. Discrete variables are summarized by frequency (%), and the differences are tested by Fisher exact test.

[a] Data are summarized by median (the 1st and the 3rd quantiles), and the differences are tested by Kruskal Wallis test.

Table 2. Blood Hemoglobin Biomarkers

Outcomes	Visit	Iron-fortified Gummy	Control	Group Difference Iron-fortified Gummy vs. Control	p-value	Differences from Baseline, p-value	
						Iron-fortified Gummy	Control
Hemoglobin, g/L	Baseline	104.7±4.7	104.0±5.2	0.7 (-1.7, 3.0)	0.564		
	Week 4	115.1±13.4	106.1±11.6	9.0 (2.9, 15.1)	0.005	<0.0001	0.113
	Week 8	120.2±9.9	105.7±10.3	14.5 (9.4, 19.5)	<0.0001	<0.0001	0.122
Mean corpuscular volume, fl	Baseline	91.7±4.8	90.3±4.3	1.4 (-0.8, 3.6)	0.195		
	Week 4	91.9±4.2	90.5±4.8	1.5 (-0.7, 3.7)	0.183	0.304	0.368
	Week 8	92.2±4.6	90.3±4.2	1.9 (-0.3, 4.1)	0.095	0.074	0.190
Mean corpuscular hemoglobin, pg	Baseline	29.3±2.3	28.7±2.2	0.6 (-0.5, 1.7)	0.265		
	Week 4	29.7±2.3	28.5±2.1	1.2 (0.1, 2.3)	0.033	0.304	0.293
	Week 8	29.9±2.3	28.5±2.2	1.3 (0.2, 2.4)	0.020	0.017	0.981
Mean corpuscular hemoglobin concentration, g/L	Baseline	322.7±5.4	321.4±5.4	1.4 (-1.2, 3.9)	0.303		
	Week 4	324.0±6.1	320.6±5.0	3.5 (0.8, 6.2)	0.013	0.026	0.370
	Week 8	325.0±5.5	321.3±5.2	3.7 (1.0, 6.4)	0.008	0.005	0.872

Data are summarized by mean±standard deviation. Inter-group differences are tested using one-way analysis of variance and presented as the differences between least-squares means (95% confidence intervals). Intra-group differences are tested using paired t-test.

Laboratory tests: Both study groups had mean hemoglobin concentrations below the normal level at baseline according to WHO standards (104.7 g/L, SD 4.7 in the iron-fortified gummy group; 104.0 g/L, SD 5.2 in the control group).

After four weeks of intervention with the iron-fortified gummy, mean blood hemoglobin concentration increased significantly and was 9.0 g/L (95% confidence interval, CI: 2.9, 15.1) higher than that in the control group (Table 2). Improvement of hemoglobin level was seen in 25 (71.4%) participants, among which 13 (37.1%) had the measurements above the WHO cut-off point (120 g/L) for anemia diagnosis. The relative risk of anemia was 0.69 (95% CI: 0.52, 0.90) compared to the control group. Significant higher concentrations were also observed for blood MCH and MCHC (p=0.033 and 0.013, respectively) in the iron-fortified gummy group. Serum iron level increased significantly from baseline and was 3.0 µmol/L (95% CI: 0.1, 5.8) higher than that of the control group (Table 3).

After eight weeks of intervention, blood hemoglobin, MCH, MCHC and serum iron levels in the iron-fortified gummy group further increased compared to baseline (Table 2 and Table 3). A total of 28 (80.0%) of these participants had improvement in hemoglobin level and anemia prevalence was reduced by 45.7%. The relative risk of anemia was 0.57 (95% CI: 0.42, 0.79) compared to the control group. In addition, the iron-fortified gummy group showed significantly higher serum iron saturation and ferritin concentration than the control group (p=0.04 and 0.047, respectively). No statistically meaningful change was observed in blood MCV, serum UIBC and TIBC of the iron-fortified gummy

group, and in all hemoglobin and iron biomarkers of the control group.

All participants tested negative for urine bilirubin, protein, glucose, ketone body, vitamin C and nitrite at all visits. The test results were normal without significant changes throughout the study period for liver and kidney function biomarkers, as well as all other measurements of urine and blood routine tests (supplemental Table S3).

Table 3. Serum Iron Biomarkers

Outcomes	Visit	Iron-fortified Gummy	Control	Group Difference Iron-fortified Gummy vs. Control	p-value	Differences from Baseline, p-value	
						Iron-fortified Gummy	Control
Unsaturated iron-binding capacity, µmol/L	Baseline	45.5±12.3	46.3±13.1	-0.8 (-6.8, 5.3)	0.805		
	Week 4	44.5±11.0	46.8±12.5	-2.3 (-8.1, 3.4)	0.419	0.063	0.885
	Week 8	43.3±11.2	46.6±13.0	-3.3 (-9.4, 2.8)	0.285	0.071	0.832
Iron, µmol/L	Baseline	14.9±5.1	14.5±6.0	0.3 (-2.3, 3.0)	0.806		
	Week 4	17.1±5.8	14.2±6.0	3.0 (0.1, 5.8)	0.044	0.026	0.770
	Week 8	18.8±6.8	14.8±5.0	4.1 (1.1, 7.1)	0.009	0.015	0.794
Transferrin Saturation, %	Baseline	26.4±11.0	25.3±12.9	1.1 (-4.6, 6.9)	0.692		
	Week 4	28.3±11.8	24.2±12.4	4.1 (-1.8, 9.9)	0.175	0.097	0.685
	Week 8	30.8±9.7	25.4±10.6	5.4 (0.3, 10.5)	0.040	0.029	0.835
Ferritin, µg/L[a]	Baseline	30.7 (10.3, 59.5)	28.7 (9.8, 51.0)	0.1 (-0.2, 0.3)	0.593		
	Week 4	35.7 (13.4, 57.8)	28.9 (10.2, 56.3)	0.1 (-0.1, 0.3)	0.453	0.173	0.984
	Week 8	52.8 (23.8, 62.8)	22.7 (12.8, 58.0)	0.2 (0.003, 0.4)	0.047	0.003	0.623
Total iron binding capacity, µmol/L	Baseline	60.0±9.8	60.7±9.1	-0.8 (-5.3, 3.8)	0.736		
	Week 4	60.5±9.1	60.3±8.6	0.2 (-4.1, 4.5)	0.931	0.775	0.328
	Week 8	61.5±9.5	59.9±9.9	1.6 (-3.3, 6.5)	0.526	0.151	0.196

Unless otherwise noted, data are summarized by mean±standard deviation. Inter-group differences are tested using one-way analysis of variance and presented as the differences between least-squares means (95% confidence intervals). Intra-group differences are tested using paired t-test.

[a]Data are presented as median (the 1st and the 3rd quantiles). Inter-group and intra-group differences are tested on log10 transformed data.

Skin Biophysical Characteristics: There was a significant increase in facial skin redness after four weeks of the iron-fortified gummy consumption. The measurement was significantly higher than that of the control group (+0.8; 95% CI: 0.1, 1.5). As study intervention continued for eight weeks, the iron-fortified gummy group showed significantly increased measurements of facial skin hydration (+2.9 µS; 0.2, 5.7) and luminance (+1.0; 0.3, 1.7), along with significant decreased TEWL (-4.7 g/m^2·h; -6.4, -0.03) compared to the control. The average

concentration of hemoglobin in the iron-fortified gummy group significantly increased from baseline. However, the test for group difference yielded no significant results (Figure 1).

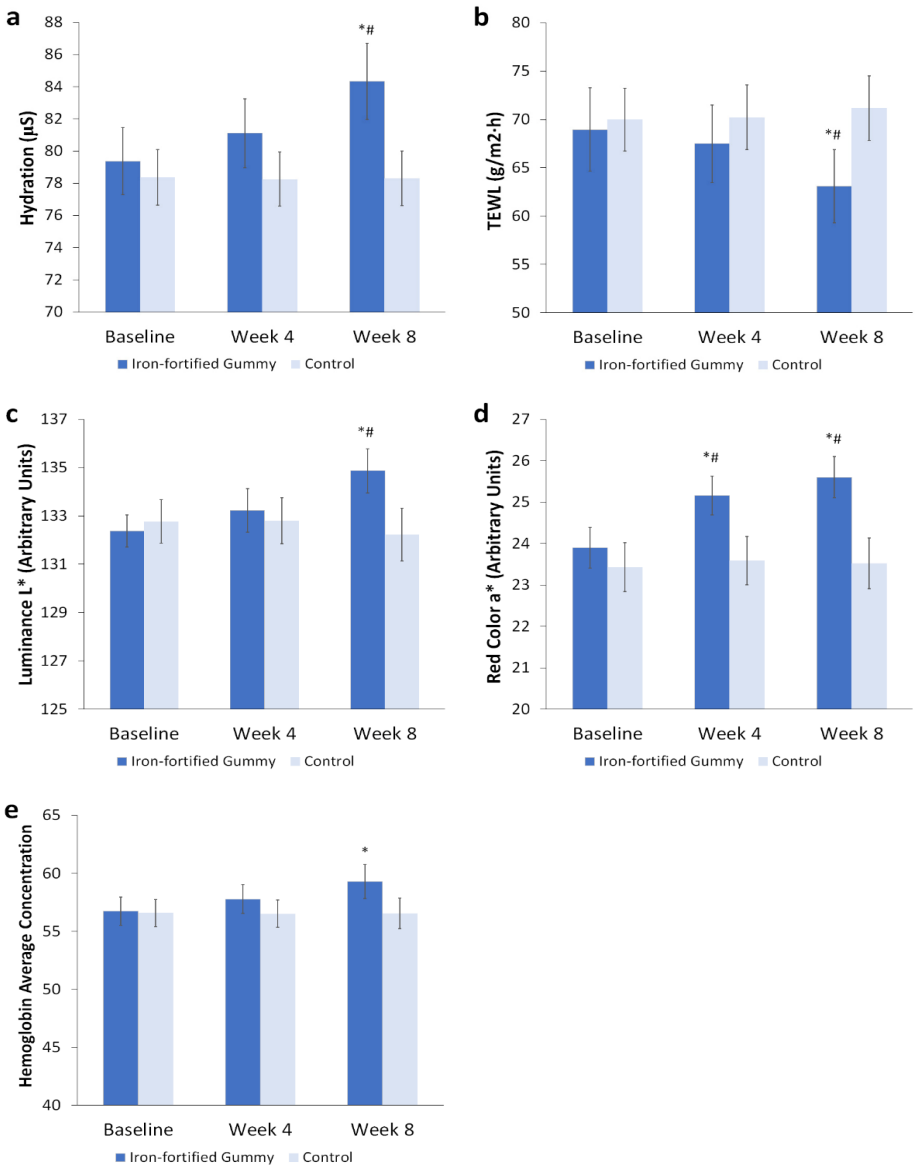


Figure 1. Facial skin biophysical characteristics. a. Hydration; b. Transepidermal water loss; c. Luminance L*; d. red color a*; e. Hemoglobin average concentration. Data shown are mean ± standard error. *: significant difference compared to the baseline. #: significant difference compared to the control. Abbreviations: TEWL, transepidermal water loss; μS, micro-Siemens.

Hand temperature recovery: The iron-fortified gummy group and the control group had similar mean hand temperature and showed no significant difference at all measurement time points at baseline. The hand temperatures of the two groups before and immediately after cold water immersion were also comparable after intervention.

Following four weeks of intervention, hand temperature recovery of participants in the iron-fortified gummy group tended to accelerate. The average temperatures of the three fingers at all measurement time points after cold water immersion were slightly higher than the values at the corresponding time points during baseline assessments, but the differences

compared to the baseline, or the control group were not significant.

The same assessments were repeated at the eighth week after intervention. Starting two minutes after cold water immersion, the hand temperatures of the iron-fortified gummy group significantly increased compared to the baseline measurements at matching time points and were significantly higher than that of the control group at all time points (Figure 3). The recovery of hand temperature for participants in the control group did not change significantly before and after the intervention.

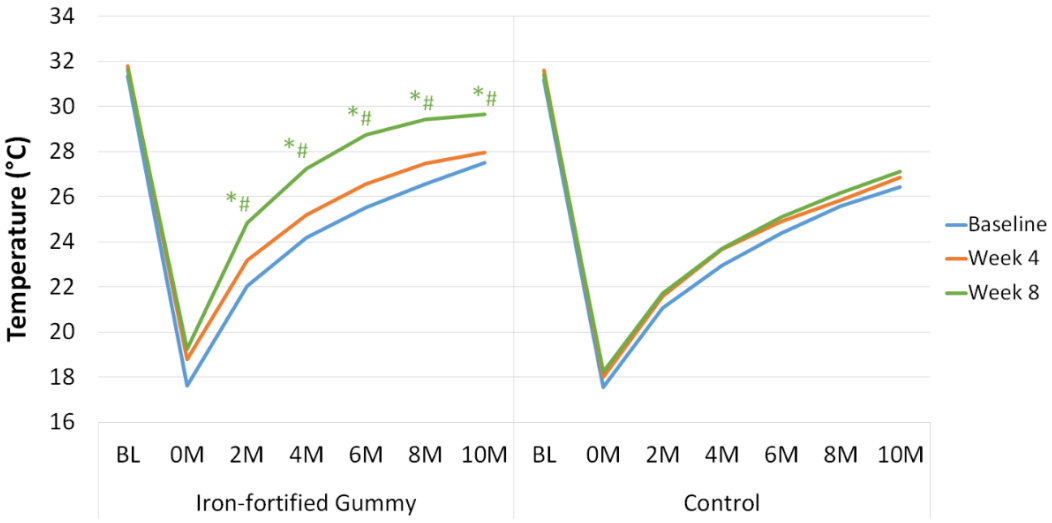


Figure 2. Change in hand temperatures. BL、0M、2M、4M、6M、8M、10M represents before, immediately after, 2, 4, 6, 8 and 10 minutes after soaking hand in cold water. *: significant difference compared to the baseline. #: significant difference compared to the control.

Self-reported outcomes: Quality of life scores in all areas were comparable between the two groups at baseline. After four weeks of intervention, the iron-fortified gummy group showed slight increases in quality-of-life scores, although the changes compared to the baseline and the control group were not significant. As the iron-fortified gummy intake continued for eight weeks, participants experienced significant improvements in their overall perception of quality of life (+0.3; 95% CI: 0.1, 0.6) and health (+0.3; 0.04, 0.7) compared to the control group. They also reported significantly higher domain score of physical health (+10.1; 5.4, 14.8) than the control (Table 4). Improvements were seen in all individual items in the physical health domain, including reduced physical pain that affect daily life, less need of medical supports, more energy and mobility to cope with daily life, increased satisfaction with sleep quality, and ability to engage in daily activities and work. In the psychological health domain, the ability to concentrate and self-satisfaction of the iron-fortified gummy group improved significantly compared to that of the control group (p=0.015 and 0.004, respectively, supplemental Table S4). In addition, participants' average daily sleep duration following the iron-fortified gummy intake increased significantly from baseline at both four weeks and eight weeks and were both significantly longer than that of the control group (p=0.038 and 0.005, respectively).

Participants in both study groups reported no major gastrointestinal symptoms, including abdominal pain, reflux, indigestion, diarrhea, and constipation. Test of inter-group differences and intra-group changes from baseline resulted in lack of significance (Table S5 of the supplemental files).

Table 4. Quality of Life and Sleep

Outcomes	Visit	Iron-fortified Gummy	Control	Group Difference Iron-fortified Gummy vs. Control	p-value	Differences from Baseline, p-value	
						Iron-fortified Gummy	Control
Overall perception of quality of life	Baseline	3.3±0.5	3.3±0.5	-0.03 (-0.3, 0.2)	0.810		
	Week 4	3.5±0.5	3.4±0.5	0.1 (-0.2, 0.3)	0.454	0.070	0.535
	Week 8	3.7±0.5	3.4±0.5	0.3 (0.1, 0.6)	0.019	0.002	0.536
Overall perception of health	Baseline	3.1±0.7	3.1±0.7	-0.1 (-0.4, 0.3)	0.734		
	Week 4	3.2±0.7	3.2±0.6	-0.01 (-0.3, 0.3)	0.938	0.169	0.475
	Week 8	3.6±0.6	3.2±0.6	0.3 (0.04, 0.7)	0.027	0.004	0.500
Physical health (PHYS)	Baseline	61.3±13.8	62.5±12.9	-1.1 (-7.5, 5.3)	0.727		
	Week 4	65.5±11.9	62.1±9.5	3.4 (-1.9, 8.6)	0.201	0.053	0.832
	Week 8	72.4±9.1	62.3±9.8	10.1 (5.4, 14.8)	<0.0001	<0.0001	0.859
Psychological health (PSYCH)	Baseline	58.5±11.1	59.9±11.9	-1.4 (-6.9, 4.1)	0.605		
	Week 4	62.1±12.1	61.9±9.2	0.3 (-4.9, 5.5)	0.917	0.066	0.250
	Week 8	65.2±9.8	60.5±9.4	4.7 (-0.1, 9.5)	0.057	0.004	0.582
Social relationships (SOCIL)	Baseline	62.6±14.1	61.7±11.7	1.0 (-5.2, 7.1)	0.759		
	Week 4	65.0±14.3	63.1±11.2	1.9 (-4.4, 8.1)	0.552	0.223	0.238
	Week 8	66.7±13.2	62.4±13.1	4.3 (-2.3, 10.9)	0.195	0.166	0.561
Environment (ENVIR)	Baseline	58.3±12.4	56.8±14.5	1.5 (-4.9, 7.9)	0.639		
	Week 4	60.4±11.2	58.1±11.3	2.3 (-3.1, 7.8)	0.400	0.162	0.382
	Week 8	61.9±10.0	58.9±8.7	3.1 (-1.6, 7.7)	0.196	0.074	0.183
Average daily duration of sleep, hour	Baseline	7.0±0.7	7.0±0.9	0.04 (-0.3, 0.4)	0.827		
	Week 4	7.4±0.8	7.0±0.8	0.4 (0.02, 0.8)	0.038	0.004	0.635
	Week 8	7.5±0.6	7.0±0.7	0.5 (0.1, 0.8)	0.005	0.001	0.845

Data are summarized by mean±sdandard deviation. Inter-group differences are tested by one-way analysis of variance and presented as the differences between least-squares means (95% confidence intervals). Intra-group differences are tested by paired t-test.

Menstruation and leucorrhea status: Participants in the two study groups had similar length of menstruation cycle, menstrual duration and leucorrhea characteristics including odor, color and volume at baseline and throughout the study period. The iron-fortified gummy group reported less headache and insomnia during menstruation compared to the control group (p=0.022 and 0.011, respectively, supplementary Table S6).

Adverse Events: A total of 14 (20.0%) AEs occurred during the study. Among them 6 (17.1%) were in the iron-fortified gummy group and 8 (22.9%) were in the control group. The AEs reported included otitis media (3), dental ulcer (1), traumatism (2), stiff neck (1), cold (3), cough with no other related symptoms (1), eczema (2) and skin rash (1) (supplementary Table S7). None of the AEs were associated with the study product, and the inter-group

difference in the overall incidence of AEs was not significant (p=0.766). There was no SAE during the study.

DISCUSSION

Anemia is a major global health problem, which affects nearly two billion people worldwide [27]. It is the only highly frequent nutritional deficiency in both developing and developed countries, and IDA is the most common type of anemia [6]. Nutrition intervention through iron-fortified foods is proven to be the most effective and feasible way to alleviate IDA symptoms [28–30]. The Functional Food Center identifies functional foods as "natural or processed foods that contain bioactive compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms" [31]. Iron fortification during food manufacturing enables the delivery of effective, small doses of the micronutrient with the possibility of multiple servings per day [32]. It increases body iron levels slower than iron supplementation or therapy but might be safer when consumed on a sustainable basis.

Our study has found that, after taking the iron-fortified gummy for four weeks, participants with moderate IDA had a significant increase in blood hemoglobin concentration compared to the baseline. As the gummy consumption continued for another four weeks, their mean blood hemoglobin level increased by 14.5 g/L compared to the control. Our findings were comparable to that from some previous studies, which reported increases of hemoglobin between 12 and 14.2 g/L in similar target groups [33–36]. Mean corpuscular hemoglobin amount and concentration in the blood also improved since the fourth week of gummy consumption.

In addition to low hemoglobin level, low ferritin is also indicative of IDA [37]. Serum ferritin is the storage molecule for iron and is therefore used to detect malfunction in cellular iron storage. A US national survey identified that physiologically based serum ferritin threshold for ID is about 24-25 µg/L for non-pregnant women of reproductive age [38]. The median serum ferritin of the iron-fortified gummy group in our study was 30.7 µg/L at baseline. It increased markedly to 52.8 µg/L by the end of the intervention, and the majority of the group had the level above the threshold for ID. Although TSAT (derived from serum iron and TIBC) is not diagnostic for ID by itself, values below 20% indicate an insufficient supply of iron for hemoglobin synthesis [39]. Our study participants with moderate IDA had a mean TSAT around 26% at baseline. Intake of the iron-fortified gummy effectively improved body iron storage, as shown by the significantly increased serum iron and TSAT.

Iron plays a critical role in the energy metabolism of most systems and organs in the human body. The commonly experienced clinical symptoms of moderate IDA include chronic fatigue, headaches, and dizziness, decreased physical activity capacity, lack of productivity, pale skin and fainting [6,37]. Due to these negative health consequences, IDA is often related to a significant decline in quality of life [40]. As consumption of the iron-fortified gummy relieved anemia, participants reported reduced physical pain, less need of medical supports, more energy and mobility for daily activities, improved sleep quality, and better ability to concentrate. All of these contributed to higher overall quality of life and health satisfaction. Improvements were also observed in participant's facial skin hydration and TEWL, suggesting a beneficial effect of the gummy on the skin barrier function [41]. In addition, participants in the iron-fortified gummy group showed heathier skin complexion and glow alongside increased hemoglobin average concentration by the end of the intervention.

Another symptom related to IDA is poor temperature regulation, especially in hands and feet [42]. This may be due to issues with both the ability of heat production and the regulation of heat loss rates. Low

oxygen levels in the body lead to competing demands between tissue oxygenation and reduced blood flow for controlling heat losses [43]. In the present study, while immediate responses of hands temperature to cold stress remained similar to baseline, iron-fortified gummy consumption effectively improved temperature recovery in hands.

Due to oxidation-reduction reactions, iron can induce unacceptable sensory changes in the food [44]. Therefore, when choosing iron carriers for fortification, a key consideration is to balance chemical stability, solubility, and bioavailability [32]. Among the four iron compounds added in the gummy under study, naturally sourced HIP is the most easily absorbable form and contributes 10% or more of our total absorbed iron [45]; pyrophosphate in FePP can enhance iron transfer from transferrin to ferritin and promote iron exchange between transferrin molecules [46]; ferrous bisglycinate allows iron absorption to be regulated physiologically by the body's iron status and is associated with fewer gastrointestinal adverse events [21,47]; NaFeEDTA remains stable during food processing and storage, and is highly bioavailable as the binding of ethylenediaminetetraacetic acid with iron partially protects the iron from the effects of inhibitors of iron absorption [48]. These properties allow them to offer a better absorption rate by the human body without modifying the individual characteristics of the food vehicle [48–50]. Participants who took the iron-fortified gummy did not experience major gastrointestinal symptoms throughout the eight weeks of intervention. Consumption of the iron-fortified gummy was not associated with any AE during the study period.

Our study was not the first randomized controlled trial that studied the effectiveness of iron-fortified foods among participants with IDA [51]. Many previous studies carried out in other countries have proven the positive effects of iron-fortified foods on alleviating IDA symptoms and on many other aspects of the user's health condition [52–58]. However, by focusing on Chinese young women with IDA, our study offers additional support for the positive health benefits of iron-fortified foods within this population. Additional studies may be conducted on other target groups such as children or pregnant women to further study the efficacy of this iron-fortified gummy. We chose the form of a soft candy as the food vehicle for iron fortification. The product is easy to consume and has a good taste, making it well accepted by the general population. Moreover, we involved non-invasive bioengineering devices which were not often seen in food nutrition studies to measure skin biophysical characteristics. Through these methods, we showed that iron supplementation not only increased body hemoglobin level, but also improved skin conditions. Despite the positive results from the present study, some limitations need to be addressed in future research. Iron absorption is affected by nutrients and compounds consumed from daily diet. While ascorbic acid, lactic acid and animal meat factors promote iron absorption, phytates in wholegrains, polyphenols in tea and coffee, proteins from soya bean, milk, eggs and calcium are known inhibitors for iron absorption [59]. Adjusted or stratified analysis with the composition of the diet concerning the content of inhibitors/promoters of iron absorption might be necessary to explore the effect of the gummy product in real world applications.

CONCLUSION

In conclusion, our findings suggested that continuous consumption of the Minayo iron-fortified gummy under study could help build up blood iron levels to generate hemoglobin and relieve IDA-related symptoms in young Chinese women. The gummy intake effectively improved skin barrier functions, skin complexions and temperature regulation in hands, and had a positive impact on the user's quality of life and satisfaction with their health. Our study showed a feasible method to deliver iron daily, gradually increase body iron levels, and provide

sustainable long-term benefits. The efficacy of the iron-fortified gummy in other target groups and its association with diet compositions require further exploration in future studies.

Abbreviations: AE: adverse event, AL T: alanine aminotransaminase, ANOVA: analysis of variance, AST: aspartate aminotransferase, BMI: body mass index, CI: confidence interval, FePP: ferric pyrophosphate, GSRS: Gastrointestinal Symptom Rating Scale, HIP: heme iron polypeptide, ID: iron deficiency, IDA: iron deficiency anemia, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, MCV: mean corpuscular volume, MET: metabolic equivalent of task, NaFeEDTA: sodium ferric ethylenediaminetetraacetate, SAE: serious adverse event, SCH: stratum corneum hydration, SD: standard deviation, SE: standard error, TEWL: transepidermal water loss, TIBC: total iron binding capacity, TSAT: transferrin saturation, UIBC: unsaturated iron binding capacity, WHO: World Health Organization, WHOQOL-BREF: World Health Organization Quality of Life-BREF.

Authors' Contribution: Yan Xiao: data curation, methodology, project administration, and writing; Bingjie Yang: data curation, methodology, project administration, and writing; Jiayi Ni: formal analysis and writing; Ran Hu: data curation, supervision, review, and editing.

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