



Limiron Granules for Iron Deficiency Anemia in School going Children

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Iron Deficiency Anemia (IDA) is leading cause of the health derangements in school going children of India. Supplementation with iron preparation has been the integral part of our primary health policies still prevalence of childhood IDA is alarmingly high even though nationwide national program and policies are implemented by GOI. Ayurveda traditional system of medicine defines the different herbo-mineral combination to treat IDA. Limiron Granules (LG) the proprietary Ayurveda medicine developed by SG Phyto Pharma Private Limited, Kolhapur Maharashtra India is used in this clinical trial for the management of childhood IDA.

Aim: Clinical trial to evaluate the role of Limiron granule in children with IDA.

Methods: Single arm Phase 3 clinical trial of this medicine has been carried out at Parul Ayurveda Hospital, Limda Vadodara, Gujarat, India. Total 104 children were enrolled in this study from rural and urban sector of Vadodara, Gujarat. Limiron granules were administered for 90 days and results were observed.

Observation and Results: Statistically significant ($p < 0.01$) results were obtain in subjective

parameters of IDA like Pallor, fatigue, anorexia, stomatitis etc. while statistically significant result were observed in blood indices like MCH, MCHC with average increment of Hb 3 g/dL and increment in Sr. Iron level.

Discussion and Conclusion: A Limiron granule is herbomineral combination containing iron in Fe₂O₃ form with Calcium in hydrate form, and natural phytosteroids. All these drugs help to promote the growth and improving the blood indices in children with IDA.

Keywords: Ayurveda; iron deficiency anemia (IDA) limiron granules (LG); proprietary ayurveda medicine; SG phytopharma.

1. INTRODUCTION

In developing countries like India, one have the burden of population explosion, poor sanitation, low per capita income, scarcity of resources and health awareness. As children are in growing phase and requiring the high demand of the nutrients the above mentioned factors affect intensely to child's nutritional status; and hence there is increased incidence of nutritional or deficiency disorders in children. Iron deficiency and Iron Deficiency Anemia (IDA) is one among them. Anemia is a condition in which the number of red blood cells or the haemoglobin concentration within them is lower than normal. Haemoglobin is needed to carry oxygen and if you have too few or abnormal red blood cells, or not enough haemoglobin, there will be a decreased capacity of the blood to carry oxygen to the body's tissues. This results in symptoms such as fatigue, weakness, dizziness and shortness of breath, among others. The optimal haemoglobin concentration needed to meet physiologic needs varies by age, sex, elevation of residence, smoking habits and pregnancy status. The most common causes of anaemia include nutritional deficiencies, particularly iron deficiency, though deficiencies in folate, vitamins B12 and Vitamin A are also important causes; haemoglobinopathies; and infectious diseases, such as malaria, tuberculosis, HIV and parasitic infections. Anemia is a serious global public health problem that particularly affects young children and pregnant women. WHO estimates that 42% of children less than 5 years of age and 40% of pregnant women worldwide are anemic [1]. Iron deficiency anemia (IDA) continues to be major public health problem in India. It is estimated that about 20% of maternal deaths are directly related to anemia and another 50% of maternal deaths are associated with it. Anemia prevalence in young children continues to remain over 70% in most parts of India and Asia despite a policy being in place [2].

Nutritional Deficiency Anemia in Children The question, therefore, is why, despite being the first country to launch the National Nutritional Anemia Prophylaxis Program in 1970, the problem of IDA remains so widespread. As is to be expected, the economic implications of IDA are also massive. The issues of control of IDA in India are multiple. Inadequate dietary intake of iron, defective iron absorption, increased iron requirements due to repeated pregnancies and lactation, poor iron reserves at birth, timing of umbilical cord clamping, timing and type of complementary food introduction, frequency of infections in children, and excessive physiological blood loss during adolescence and pregnancy are some of the causes responsible for the high prevalence of anemia in India. Even after the nationwide policies and National Program run by Government of India; IDA is one of the national health issues in children. Hence the researches in alternative herbal medicines is going on everywhere at different sites.

Ayurveda traditional system of Indian medicines defines the *Pandu Roga* as one of the disease which resembles the anemia and hence the treatment protocols of the *Pandu Roga* are applicable in treatment of IDA. There are certain Ayurveda herbal medicines which are helpful to improve the iron level in human body and can be definitely use in the treatment of IDA. In India one Proprietary combination known as Limiron Granules prepared by SGS Phytopharma from Kolhapur Maharashtra, which contains Ayurveda herbs and *Mandoora Bhasma* (One form of organic Iron) and hence we have taken this combination for the therapeutic treatment of iron deficiency and iron deficiency anemia.

2. RESEARCH DESIGN

The methodology intended for the study is as per the Consolidated Standards of Reporting Trials (CONSORT) statement2010 and WHO GCP guideline. The clinical trial was designed to assess the efficacy of Proprietary Ayurvedic

medicine Limiron Granules in Iron Deficiency Anemia (IDA) in children.

Interventional, Single Arm Clinical Trial (**Phase of Trial- Phase 4**) on patients of Deficiency Anemia (IDA) of sample size 100. The trial is registered in CTRI wide ref-CTRI/2019/05/018963 [Registered on: 06/05/2019].

Principal investigator- Dr Swapnil CR, Associate Professor of Kaumarbhritya, Monetary and material support is by- SG Phyto Pharma Private Limited 532/1, Nilgiri Apartment, Plot no.3, "E", Rajendranagar ring Road, Kolhapur- 416004/1. Maharashtra- India.

2.1 Eligibility/ Inclusion Criteria

1. Age - From 5.00 Year(s) Age To 12.00 Year(s)
2. Gender - Both
3. Children having classical features of iron deficiency anemia like, Pallor, fatigue palpitations exertional dyspnea etc.
4. Hb less than 11.5 g/dl and not less than 7.5 g/dl

2.2 Exclusion Criteria

1. Children less than 5 years and more than 12 years of age
2. Children with other metabolic and endocrinal disorders
3. Children with other causes of Anemia like hemoglobino pathies
4. (Thalassemia's and sickle cell anemia)
5. Children suffering from infectious diseases like TB Hepatitis leukemia

Patients fulfilling the criteria for diagnosis was included in the study and subjected to thorough interrogation and physical examination.

2.3 Laboratory Investigations

The following basic studies were carried out on all included subjects in order to rule out other causes of anemia and to assess the impact of the therapy;

- Hb, Complete blood cell count
- Serum Iron
- TIBC – Total Iron binding Capacity
- Serum Ferritin
- Peripheral Smear Showing

- MCV – Mean Corpuscular Volume
- MCH – Mean Corpuscular Hemoglobin
- MCHC - Mean Corpuscular Hemoglobin Concentration

History and other relevant important data was recorded in special clinical research proforma.

2.4 Interventions

Sample size (n) -Minimum 100 completing the schedule

Drug-Proprietary Ayurvedic medicine Limiron Granules

Dosage - 1-2tsp early morning empty stomach with milk

Anupana- Milk

Duration - 3 months

2.5 Limiron Granules – Product details

Drug Name	Scientific Name	Proportion
Shatavari root	Asparagus racemosus	200 mg
Mandoor Bhamsa	Processed Ferrioxidum	100 mg
Khajur	Phoenix digitata	150 mg
Kukkutandatwak Bhamsa	Generic Preparation	250 mg
Buikohala	Ipomoea digitata	100 mg
Sugar	Sugar Candy	Q.S. to 5

2.6 Primary Outcome

1. Attain at least 1.5 g/dl increment in Hemoglobin than baseline reading of Hb% (before treatment) - At 12 weeks reduction in pallor and other symptoms at 12 weeks
2. Reduction in pallor and other symptoms like fatigue, leg cramps

2.7 Secondary Outcome

1. Weight gain at least 3 kg in 60 days

3. RESULTS AND OBSERVATION

After administration of Limiron granules in recommended doses it has been observed that there average (31%) 3.1g/dl improvement in Hb % while 18% i.e. 54000 ccm improvement in TRBCs count; 32% i.e. increment of PCV by 8. In addition improvement in MCV [increase volume of RBC by 19fL (27%)], MCH [increase Hb per

RBC by 3.5pg (18%), MCHC [increase volume of RBC by 2.2pg/fL (27%)], while improvement in Sr Iron [average increase by 17 mcg (40%)]. All these improvement in blood indices was found to

be statistically significant. Improvement in TIBC (Total Iron Binding Capacity) and Serum Ferritin was found to be statistically insignificant.

Table 1. Results on Hematological parameters

I - HEMATOLOGICAL PARAMETERS					
Sr. No.	Parameter	Average Improvement	Percentage	Significance	p value
1	Hb	Ave 3.1 g/dl	31%	S	p < 0.01
2	RBCs	54000	18%	S	p < 0.01
3	PCV	8	32%	HS	p < 0.01
4	MCV	19 fL	27%	S	p < 0.01
5	MCH	3.5 pg	18%	S	p < 0.01
6	MCHC	2.2 pg/fL	27%	HS	p < 0.01
7	S IRON	17 mcg	40%	HS	p < 0.01
8	TIBC	57	38%	NS	p > 0.01
9	S FERRITIN	62	37%	NS	p > 0.01

Table 2. Results on Anthropometrical parameters

II-ANTHROPOMETRY PARAMETERS					
Sr. No.	Parameter	Average Improvement	Percentage	Significance	p value
1	WT	2KG	9%	S	p < 0.01
2	MUAC	1.2cm	8%	S	p < 0.01
3	BMI	1.46KG/m2	10%	S	p < 0.01

Table 3. Results on Subjective parameters

III - SUBJECTIVE PARAMETERS					
Sr. No.	Parameter	Mean Diff	Percentage	Significance	p value
1	Pallor	2.5	94%	S	p < 0.01
2	G Weakness	3	95%	NS	p > 0.01
3	EX Dyspnea	1.5	85%	NS	p > 0.01
4	Leg Cramps	3	94%	NS	p > 0.01
5	Loss of Appetite	3	89%	NS	p > 0.01
6	Stomatitis	2	94%	NS	p > 0.01
7	Hair Loss	3	90%	S	p < 0.01

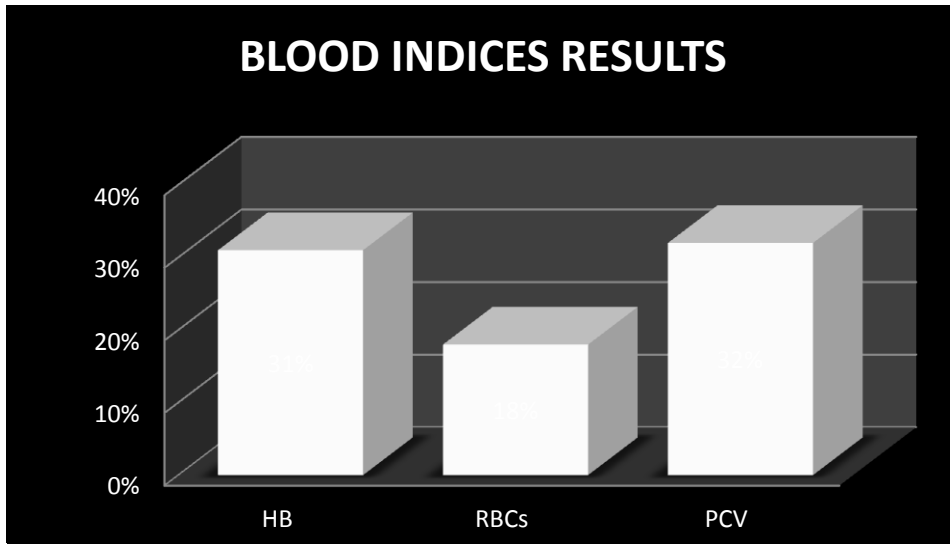
There is statistically significant improvement in gaining weight, BMI (Body Mass Index) and MUAC9 (Mid Upper Arm Circumference). Average increment in parameter is shown in Table 2.

The average mean value for Hb (BT) is observed 9.3 g/dL while it has been observed to be 12.5

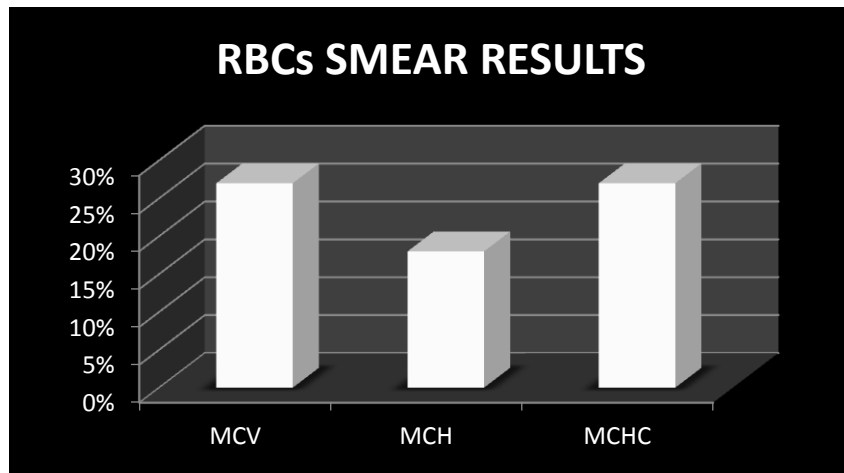
g/dL (AT), which is statically significant with paired "t" test.

There is good percentage of improvement in the clinical features of the IDA after administration of *LimironGranules* to school going children.

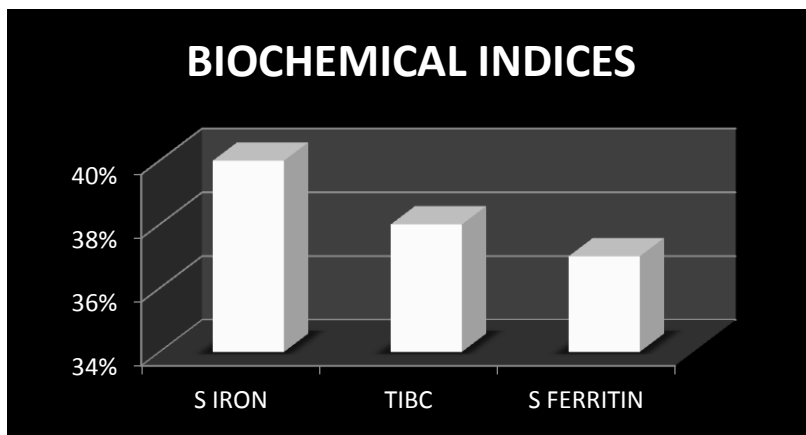
4. GRAPH PRESENTATION



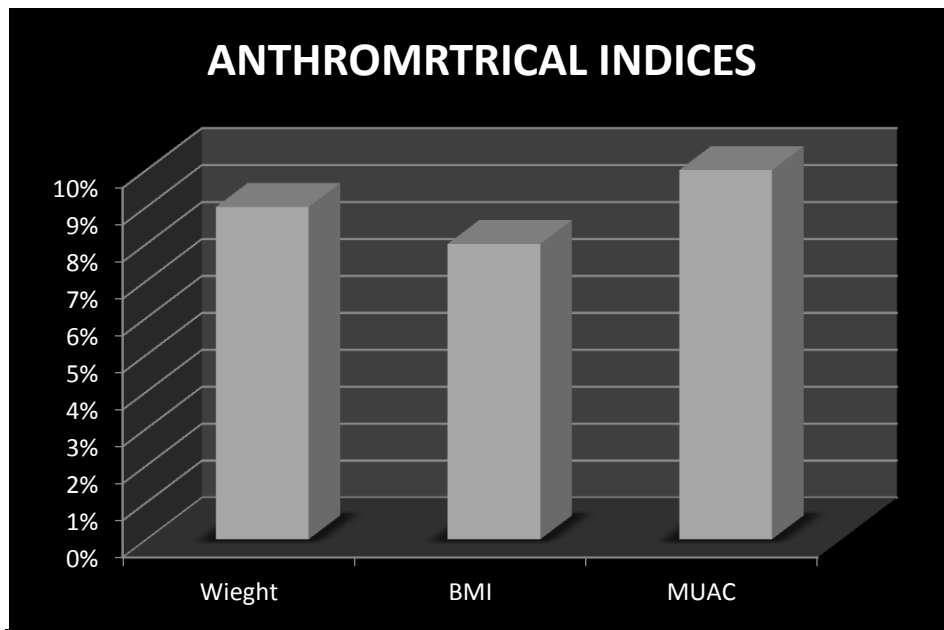
Graph 1. Percentage improvement in hematological indices



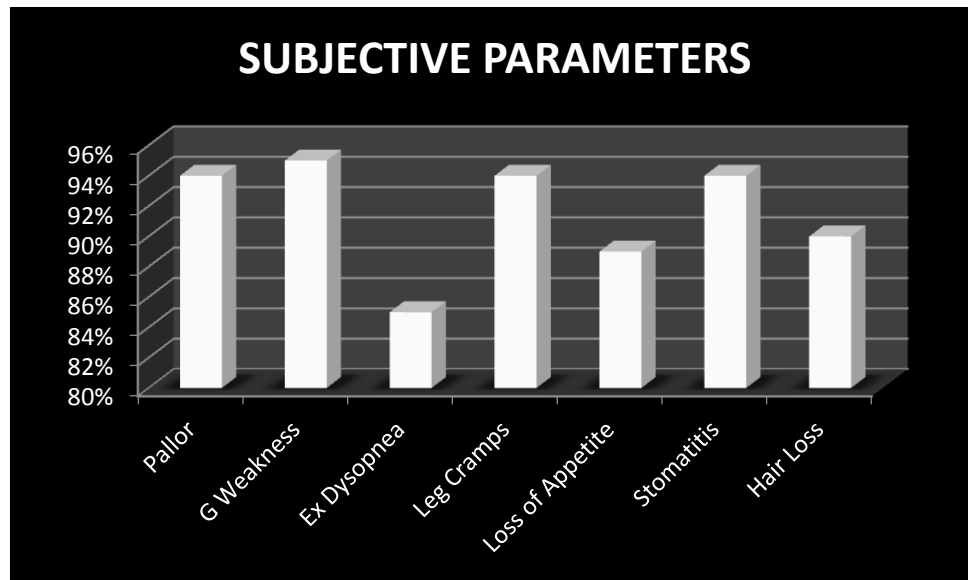
Graph 2. Percentage improvement in RBC Morphological indices



Graph 3. Percentage improvement in biochemical indices



Graph 4. Percentage improvement in Anthropometrical indices



Graph 5. Percentage improvement in Subjective Parameters of IDA

5. DISCUSSION

5.1 Discussion on Methodology

It is a clinical study with pre- test and post- test design conducted in single group. Total 104 patients were enrolled in this study from OPD and IPD of Parul Ayurveda hospital. Out of that 104 patients were completed the treatment. Were follow up for a period of 4 weeks and assessment was done after 3

months on the basis of subjective and objective criteria before and after treatment.

5.2 Observations after Follow up

After the active treatments, patients were monitored for another 2 weeks for the occurrence of recurrence in signs and symptoms of Iron Deficiency to find out the sustained effect of therapy.

5.3 Adverse Drug Reactions

No Adverse drug reaction attributable to the trial/control drugs was reported during the study.

5.4 Withdrawals

None of the subjects were required to be withdrawn from the study as there was no serious health condition requiring referral occurred during the study period.

5.5 Rescue Medications

No rescue medications were used during the study as it was not warranted.

5.6 Discussion on Pharmacological action of ingredients of *Limiron Granules* in Iron deficiency of Anemia

All the drug of LIMIRON granules showed the synergistic effect in increasing the Serum Iron level and relieving the symptoms of clinical features of IDA. Drugs like *Shatavari*, *Kharjura* and *Vidari* having anti-oxidant properties which reduces the oxidative stress and help to improve the process of hemopoiesis and helps to stabilize the membrane of RBCs and hence improving the life span and membrane stability of RBCs. In addition these drugs help to maintain the growth of RBCs and hence there is improvement in the MCV. *Kharjura* and *Mandoora* having rich source of Iron which helps to increase the MCH and MCHC with improvement in serum Iron level.

5.7 Few Evidence based Researches

The oral administration of extract *Asparagus racemosus* root in the dose of 750 mg/kg/day essentially increased RBC count and hemoglobin level and decline WBC count. *Asparagus racemosum* have shown anti-anemic properties [3,4,5,6,7]

6. VIDARI [8]

Activity	Constituents	Structure
Anti-oxidant	Puerarin	
Antimicrobial activity	Eicosanoic acid	
Wound-healing activity	Hydroxytuberosone	
Anti-inflammatory activity	Biochanin A	

Mandura Bhasma possesses significant haematinic and cytoprotective activity [9] *Mandoor Parpati* may reduce the risk of aplastic and iron deficiency anaemia [10]. Though there are some articles on the toxicity of the Ayurveda iron preparations by some research scholars of physics [11] it is well evident that, there is definitely no toxic effect of Mandoora Bhasma when prepared and administered scientifically in permissible limits. Hematinic role of Mandoor is well known [12].

The augmentation of body mass during neonatal and childhood growth spurts transiently boosts iron requirements (Gibson et al., 1988) [13] Results on subjective parameters of iron deficiency and IDA showed improvement in all subjective parameters along with hematological blood indices [14].

Mandur bhasma works as Anti-oxidant, anti-inflammatory, mild-laxative, it helps in reducing the free radical production and inflammations from the cells which help in enhance cell survival thereby improving the condition of anemia [15] Magnetic iron calx is used in treatment of [16] Subjective parameters result [17]

As the deficiency of iron, is the chief course to develop anemia, prime importance should be given to supplement the body with extra iron. Hence *Mandur bhasma* is used in this preparation which is easy to digest with less known adverse effects, than that of iron, and it is also can be used in children and females safely [18]

Kharjura which is one of the nutritious fruit rich in minerals such as Calcium, Magnesium, Potassium, Iron and also contains Vitamin B1, B2, B3, B6 and Vitamin C. *Kharjura* is having *Brumhana*, *Balya* properties and used both as food and therapeutic supplement [19] The consumption of date fruit increased hemoglobin, hematocrit, and serum ferritin levels in primary school girl students with IDA; therefore, it is recommended to give dates to school girls [20,21].

6.1 Kukkutand Twak Bhasma

An average particle size was found as 9.35 µm and 9.97 µm in samples KTB-A and KTB-B, respectively. XRD study reveals that raw *Kukkutanda Twak* is CaCO₃ (calcite) and CaCO₃ (calcium carbonate) whereas both the Bhasma contain Calcium hydride CaH₂ O₂ (portlandite

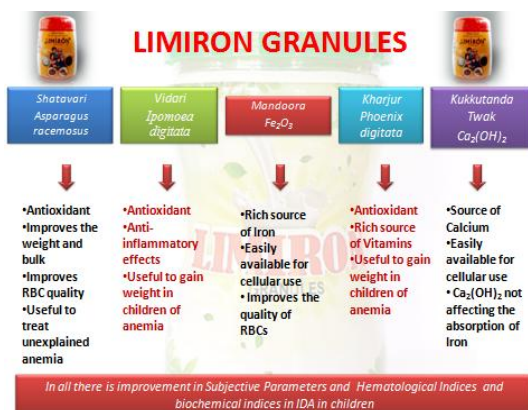
syn) and Calcium hydroxide- Ca (OH)₂. [22]. X-Ray Diffraction (XRD) analysis of the prepared bhasma from both the methods shows presence of CaCO₃ [23].

Constituents	Quantity
Calcium Carbonate (CaCO ₃)	95%
Calcium Phosphate, Magnesium Carbonate, Proteins (Soluble and Insoluble), etc.	5%

6.2 Key Points to Highlight on Ca-Fe absorption – Facts

Studies on human subjects have shown that calcium (Ca) can inhibit iron (Fe) absorption, regardless of whether it is given as Ca salts or in dairy products. This has caused concern as increased Ca intake commonly is recommended for children and women, the same populations that are at risk of Fe deficiency. However, a thorough review of studies on humans in which Ca intake was substantially increased for long periods shows no changes in hematological measures or indicators of iron status. Thus, the inhibitory effect may be of short duration and there also may be compensatory mechanisms. The interaction between Ca and Fe may be a luminal event, affecting Fe uptake through DMT1 (divalent metal transporter 1) at the apical membrane. However, it is also possible that inhibition occurs during Fe transfer into circulation, suggesting roles for the serosal

6.3 Probable Mode of Action of LIMIRON Granules in IDA in Children



7. SUMMARY AND CONCLUSION

Limiron Granule is popular iron herbo-mineral supplement and growth promoter and is found to be significant in alleviating the symptoms of IDA

exporter ferroportin (FPN) and hephaestin. We explored these possibilities in human intestinal Caco-2 cells cultured in monolayers. Iron transport ((⁵⁹ Fe) and expression of DMT1, FPN, and hephaestin were assessed after 1.5 and 4 hours with 0 or 100 μM CaCl₂. Although Ca did not affect Fe uptake or DMT1 expression at 1.5 hours, FPN abundance at the basolateral membrane decreased, resulting in increased cellular Fe retention and decreased Fe efflux. After 4 hours, DMT1 and FPN expression increased and there was increased FPN at the membrane, suggesting a rebound effect. Thus, the effect of Ca on Fe absorption may be of short duration and adaptation may occur with time. This may explain why studies on long-term Ca supplementation of different groups fail to show any adverse effects on Fe status [24].

From this discussion it is also evident that there is no direct role of Calcium in long term use on ferrous absorption. Secondly there are different forms of iron as well as calcium present in Limiron granules with plant alkaloids and hence there is no effect of calcium present in the combination affecting the iron absorption and assimilation.

“In all there from above statistical data and evidence based references it is clear that there is definite role of Limiron granules in improving the iron deficiency status in school going children.”

along with the improvement in blood indices in school going children.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge.

CONSENT

An informed written consent was obtained from all included subjects. The consent form was prepared in Accordance with the guidelines of WHO Research Ethics Review Committee (ERC).

ETHICAL APPROVAL

The study has obtained Ethical Clearance wide-PU/PIA/IECHR/2019/77.

NOTE

The study highlights the efficacy of "Ayurveda" which is an ancient tradition, used in India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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