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Evaluation of *Punarnavadi Mandura* in the management of anaemia: A community-based, single-arm, open-label, multicentric interventional study

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Anaemia is a significant global health issue, primarily impacting women and children. The most common type of anaemia is iron deficiency anaemia, which is usually treated with iron supplements. However, adherence and tolerability may be challenging due to potential gastrointestinal side effects. The symptoms of anaemia resemble those described in Ayurvedic literature as *Pandu Roga*. Ayurvedic formulations may provide a safe and tolerable alternative to conventional treatments. This study aimed to evaluate *Punarnavadi Mandura* in the management of anaemia through a community-based, multicenter, open-label clinical study. Participants of any gender aged 18 to 55 years with haemoglobin concentrations between 8 and 10 g/dL were enrolled in the study according to the selection criteria. *Punarnavadi Mandura* 500 mg was given orally with water twice daily after food for 12 weeks. The assessment was done every 4 weeks during treatment, and 4 weeks post-intervention. The haemoglobin concentration and Functional Assessment of Chronic Illness Therapy-Fatigue scores increased ($p<0.001$), while disease-specific symptoms significantly reduced ($p<0.001$) during treatment. These effects were sustained at the 4-week post-intervention follow-up without further treatment, and the medication was well tolerated by participants. The study shows that *Punarnavadi Mandura* is beneficial for managing anaemia and is well-tolerated with no serious adverse events reported. As this study was limited to an open-label single-arm trial, further randomized controlled trials are recommended to validate the results.

Keywords: Ayurveda, FACIT fatigue scale, Haemoglobin, *Pandu*

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Anaemia is a major public health challenge globally, and is characterized by a lower concentration of haemoglobin in the blood. Anaemia has a significant impact on human health as well as socio-economic development and is estimated to account for close to 9% of the total global disability burden from all ailments[1]. As per the National Family Health Survey 5 (2019–21), anaemia affects 25% of men and 57% of women in India aged 15 and 49 years[2,3]. The number of anaemia cases is higher in low and lower-middle-income nations, particularly among persons living in rural areas, poorer households, and without a formal education[4]. Anaemia is one of the leading causes of several health problems, especially in children and pregnant women. Nutritional deficiency is a major cause of anaemia as it leads to inadequate absorption of

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nutrients such as iron and folic acid, impairing erythrocytes and haemoglobin synthesis. The consequences of anaemia include decreased job productivity in adults and delayed cognitive development in children. When it occurs during pregnancy, it leads to poor birth outcomes, including low birth weight and prematurity, as well as poor cognitive and motor outcomes in newborns[1]. Studies conducted in the public health sector have reported a higher prevalence of anaemia (more than 55%) among women and children from scheduled castes (SC), scheduled tribes (ST), and backward castes compared to the general categories, since these groups typically experience poor living conditions, inadequate dietary intake, and limited access to healthcare services[5-7]. This points to the need for interventions in underprivileged communities. Conventional management of anaemia mainly focuses on oral iron and/or folic acid supplements, intravenous iron preparations, and blood transfusions. Intravenous iron supplements are used if oral supplements are ineffective or intestinal absorption is impaired. Blood transfusion is applicable only in haemodynamically unstable cases, such as patients with critical anaemia, acute myocardial ischemia, etc. Oral iron supplements are the first choice in cases of chronic anaemia without absorption anomalies because they are readily available over the counter, inexpensive, and convenient to take. Nevertheless, they may impede patient compliance and adherence by causing undesirable dose-dependent gastrointestinal symptoms, such as nausea, vomiting, abdominal discomfort, and constipation[8,9]. Furthermore, they may cause mucosal damage or a possible aggravation of the symptoms of inflammatory bowel disorders. Data from animal research shows that these supplements may have tumorigenic potential and may lead to an alteration of the gut microbiota[10].

Pandu Roga, described in Ayurvedic classics, presents symptoms that closely resemble those of anaemia. The classical textbooks of Ayurveda describe several polyherbal and herbo-mineral, formulations- particularly those containing iron-rich mineral components- for the treatment of *Pandu Roga*. Studies suggest that Ayurvedic formulations could be a safe and effective alternative to modern iron supplements for the management of iron deficiency[11]. *Punarnavadi Mandura*, one among various *Mandura* and *Lauha* based formulations, was selected due to its comprehensive composition, combining *Mandura Bhasma* with ingredients such as *Triphala, Trikatu,* and *Amalaki,* which are known to support digestion, enhance bio-availability, and improve absorption[12]. This formulation is widely used in community-based settings. The data from the animal studies have demonstrated significant cytoprotective and hematinic activity of *Punarnavadi Mandura* in mercuric chloride-induced anaemia in albino rats[13].A toxicology study performed on Wistar rats demonstrated that *Punarnavadi Mandura*, administered at a dosage of 450 mg/kg, produced no observable adverse effects[14]. Few clinical studies with smaller sample sizes have reported significant improvement in anemia with this drug and demonstrated its safety[15,16]. However, clinical trials involving large sample sizes and multicenter study settings have not been done yet. This study was designed as a community-based study to evaluate *Punarnavadi Mandura* in anaemia using a multicenter study setting and a larger sample size.

The primary objective of the study was to evaluate the effect of *Punarnavadi Mandura* in managing anaemia (*Pandu*) over a period of 12 weeks. The secondary objectives were to assess, changes in the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale and disease-specific symptoms, and to evaluate the tolerability of the formulation in the participants.

Materials and Methods

Study design

The study was designed as a single-arm, open-label, prospective, multi-centric and community-based interventional study.

Study setting

The study was conducted in Scheduled Caste (SC)-dominant areas located near the ten peripheral institutes of Central Council for Research in Ayurvedic Sciences (CCRAS) in Bengaluru, Bhubaneswar, Chennai, Cheruthuruthy, Delhi, Jaipur, Kolkata, Mumbai, Patna and Trivandrum.

Study population

Inclusion criteria

Individuals of any gender in the age group of 18 to 55 years belonging to the SC community with haemoglobin concentration ranging from 8 to 10 g/dL were enrolled in the study.

Exclusion criteria

Participants with a recent history of blood loss from the gastrointestinal system or other sources in the form

of hematemesis, melena, bleeding piles, hemoptysis, menorrhagia, history or evidence of intestinal malabsorption, major comorbidities like chronic renal, hepatic, cardiac, or pulmonary diseases, etc. were excluded from the study. Diagnosed cases of sickle cell anaemia, thalassemia, other types of hemolytic anaemia, bone marrow failure, myelodysplastic syndromes, cancer, etc. were not included. Participants who were on prolonged (>6 weeks) medication for any chronic diseases and those who were taking iron supplements (at the time or during the last 3 months of screening) were also excluded. Pregnant or lactating women or women who were planning for conception were not enrolled in the study.

Withdrawal criteria

The participants were free to leave the study if they wanted to withdraw, or if the condition worsened or in case of development of any other health ailments mentioned in the exclusion criteria during the study.

Study procedure

The screening for anaemia was conducted in SC-dominant areas located near the study centres through outreach OPD and medical camps after obtaining permission from local administrative authorities. The participants those fulfilling the pre-defined selection criteria were enrolled in the study. Follow-up assessments were conducted every 4 weeks up to 12 weeks and 4 weeks post-intervention. The data was recorded in the predefined case proforma. The participants were asked to inform any new or worsening symptoms, and details were recorded in the Case Record Form. Haemoglobin concentration was assessed during every visit starting from the screening up to 16th week. The study procedure and study schedule are depicted in (Fig. 1 & Fig. 2).

Intervention

Punarnavadi Mandura was procured from a Good Manufacturing Practices certified manufacturer-Indian Medicines Pharmaceutical Corporation Limited, Ministry of AYUSH, Government of India. The study drug was given in a dose of 500 mg twice daily orally, just after food with water for 12 weeks.

Outcome measures

The mean change in haemoglobin concentration was the primary outcome measure for the study, and was assessed at baseline, 4th, 8th, 12th and 16th weeks. Secondary outcome measures included any changes in disease-specific symptoms, FACIT fatigue scale scores, and drug tolerability. The FACIT Fatigue Scale was used to assess quality of life. A score of less than 30 indicates severe fatigue, and the higher the score, the better the quality of life. Clinical assessment of disease-specific symptoms associated with anaemia such as *Daurbalya* (weakness), *Kopanatvam* (anger/irritability), *Vaivarnyam* (pallor), *Sotham* (oedema), *Hridaya spandana* (palpitation), *Aruchi* (tastelessness), *Sirasoola* (headache), *Srama* (exhaustion/fatigue), *Bhrama* (giddiness/dizziness/ vertigo), *Karnakshweda* (tinnitus/ constant flute-like sound in the ear), *Swasa* (shortness of breath), *Mrit Bhakshana* (Pica), Koilonychia, Glossitis, and angular stomatitis was done. The assessment of the FACIT fatigue scale and disease-specific symptoms was done at baseline, 4th, 8th, 12th and 16th week. The tolerability was assessed by the proportion of recruited participants who completed the study, and occurrence of any adverse drug reaction or serious adverse event.

Sample size

The sample size was estimated assuming a mean increase of 0.9 g/dL in the haemoglobin levels between pre and post-test assessment, based on previous studies, with a standard deviation of 2.25 g/dL, at 95% Confidence Level ($\alpha = 0.05$; $Z\ 1-\alpha/2 = 1.96$) and 80% statistical power ($Z1-\beta = 0.8416$). The calculated sample size was 40 participants per centre. Assuming an anticipated 20% dropout rate, the required sample size was 48, which was rounded up to 50 participants per centre. Accordingly, the total sample size for the study was determined to be 500 participants across all ten centres.

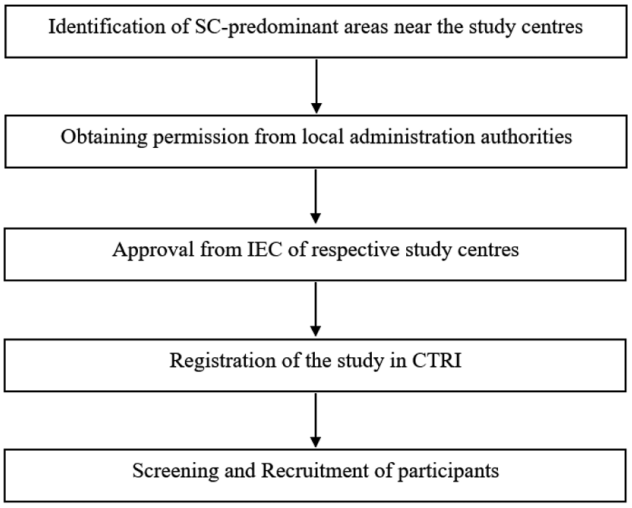

Fig. 1 — Flow diagram depicting the study procedure for the evaluation of *Punarnavadi Mandura* in Anaemia

Statistical analysis

The data was analyzed using SPSS software version 26.0. The continuous data, such as a change in haemoglobin concentration and FACIT score, was summarized as mean (standard deviation) and compared using the repeated measures ANOVA test. All the qualitative data such as changes in disease-specific symptoms during the study period were presented as numbers (percentages) and compared using the Cochrane Q-test. The level of significance during data analysis was set at 5%.

Results

A total of 4540 individuals were screened across different centres, and 485 participants with haemoglobin concentrations ranging from 8 to 10 g/dL were enrolled as per the selection criteria. Minor shortfalls in recruitment at some centres were due to operational logistical constraints. Of the 485 participants, 37 discontinued the treatment during the study period and 448 completed the study. Statistical analysis was carried out for all the participants who completed the study. The flow of participants during the study is shown in (Fig. 3).

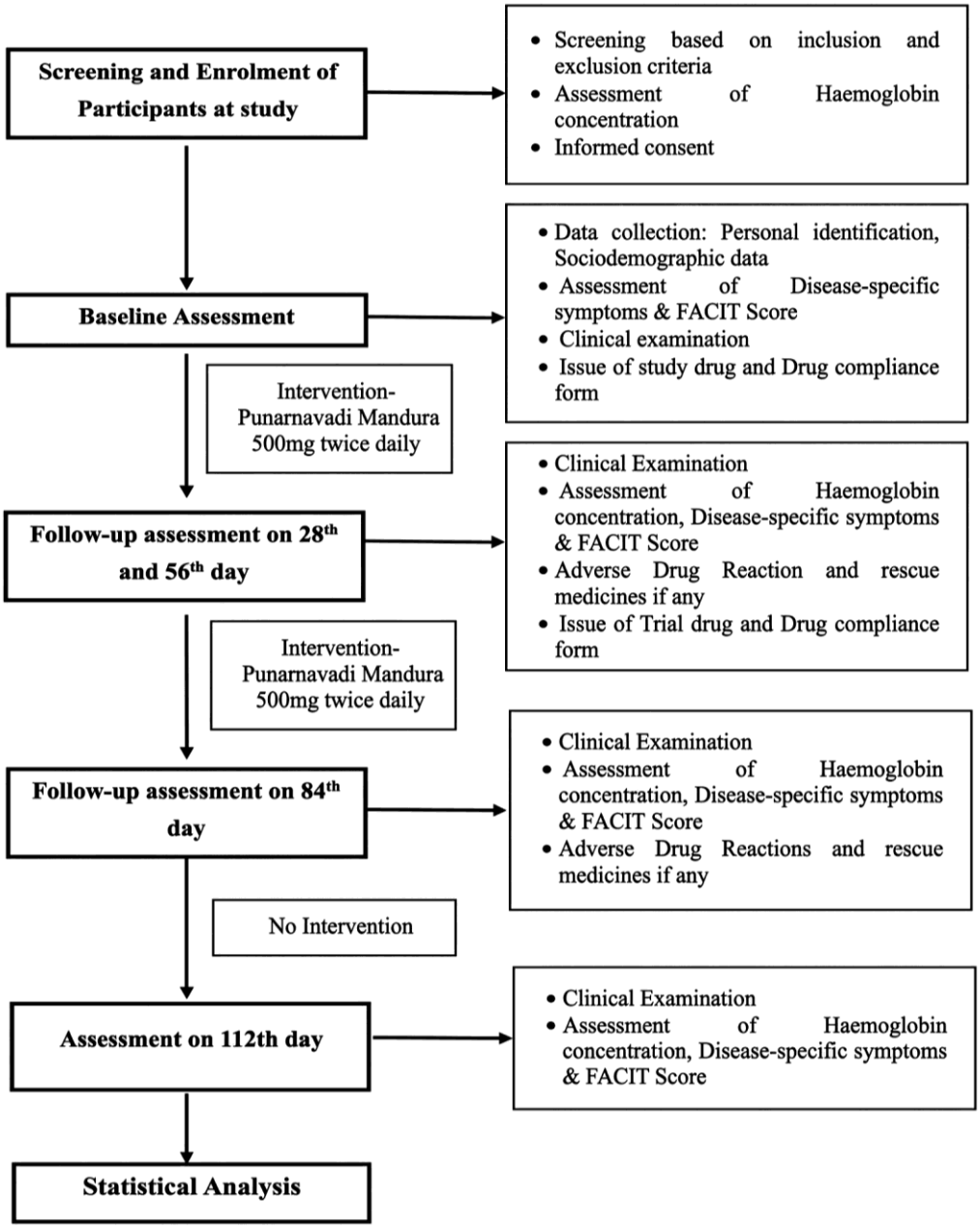

Fig. 2 — Flow diagram depicting the study schedule for the evaluation of *Punarnavadi Mandura* in Anaemia

Observation on socio-demographic and baseline data

The data analysis shows that most participants were females (94.6%). The number of participants was more in the age groups 36-45 years (31.3%) and 46-55 years (31.8%). More cases were from the lower socioeconomic class (61.4%). Most participants were involved in household work (67%) and moderate physical activities (65.2%). The data on emotional stress suggest that 52.8% of participants had moderate (40.2%) and too much stress (12.6%). In this study, most of the participants were following a non-vegetarian diet (81.9%). (Table 1) Most of the participants had weakness (96%), fatigue (81.5%), pallor (79%), headache (67.6%), anorexia (64.5), irritability (62.5%) and dizziness (60.7%), palpitation (58.5%) and shortness of breath (58%) as major presenting complaints. Symptoms such as pica (23.2%), glossitis (17.9%) angular stomatitis (14.5%) and koilonychia (10.9%) were present in a lesser percentage of people.

Table 1 — Socio-demographic & baseline data of the participants in the study

Sl. No.	Variables (n=485)		N (%)
1	Age	18-25	58 (12.0)
		26-35	121 (24.9)
		36-45	152 (31.3)
		46-55	154 (31.8)
2	Gender	Female	459 (94.6)
		Male	26 (5.4)
3	Socio economic status	Above poverty line	187 (38.6)
		Below poverty line	298 (61.4)
4	Educational status	No formal schooling	52 (10.7)
		Less than primary school	80 (16.5)
		Primary school	79 (16.3)
		Middle school	58 (12.0)
		High school	122 (25.2)
		Intermediate	66 (13.6)
		Graduate & above	28 (5.8)
5	Occupation	Household work	325 (67.0)
		Fieldwork (physical labour)	78 (16.1)
		Field Work (No physical labour)	34 (7.0)
		Desk work	48 (9.9)
6	Dietary habits	Vegetarian	88 (18.1)
		Non- Vegetarian	397 (81.9)
7	Addictions	Tobacco Chewing	25 (5.2)
		Others	6 (1.2)
		None	454 (93.6)
8	Physical Exercise	Heavy labour	43 (8.8)
		Moderate labour	316 (65.2)
		Office job	18 (3.7)
		Sedentary	108 (22.3)

Observations regarding the effect of intervention on outcome measures

The mean haemoglobin concentration of the participants increased significantly ($p<0.001$) from 9.3±0.73 to 11.1±1.71 on day 84, and was sustained at 11.2±1.51 on day 112 after a period without treatment (Table 2).

The FACIT fatigue score showed a significant improvement ($p<0.001$) during treatment, increasing from a mean of 30.6±9.22 at baseline to 42.8±7.49 on day 84 and was sustained at 43.6±7.40 after a follow-up without intervention. (Table 2).

The effect size (mean difference) for haemoglobin level from baseline to Day 84 was 1.88 g/dL (standard error 0.079), and for the FACIT score, the mean difference was 12.2 (standard error 0.382).

All disease-specific symptoms decreased significantly ($p<0.001$) from the baseline to day 84 and the effect remained sustained on day 112. The data on the change in symptoms during the treatment period is presented in (Fig. 4).

After the treatment, factors such as sleep, bowel movements, appetite, and stool consistency improved

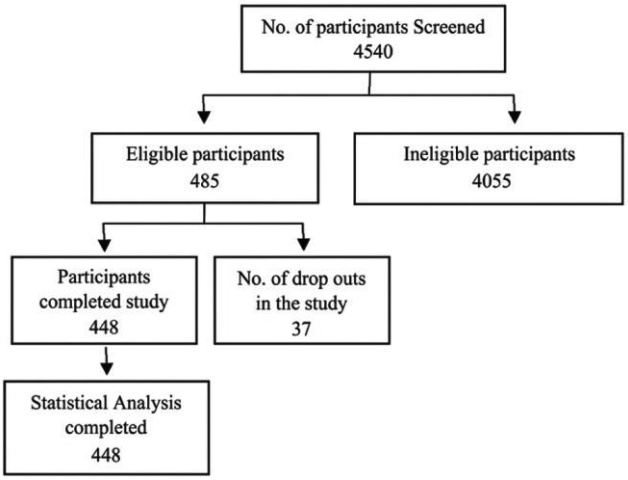

Fig. 3 — CONSORT flow chart depicting the outflow of participants in the study

Table 2 — Effect of intervention on haemoglobin and FACIT score

Assessment Criteria ^(n=446) [Mean(SD)]	Baseline	28th Day	56th Day	84th Day	112th Day	p-value
Haemoglobin	9.3 (0.73)	9.7 (0.80)	10.2 (0.97)	11.1 (1.70)	11.2 (1.51)	<0.001
FACIT Score	30.6 (9.22)	35.2 (9.53)	38.8 (9.67)	42.8 (7.49)	43.6 (7.40)	<0.001

Compared using Repeated Measures ANOVA.*p-value is significant at a 5% level of significance
^Data of 2 participants was not available for the given parameters

significantly ($p<0.001$), and these improvements persisted during the follow-up period as well. At the beginning of the study, 38.6% of participants had disturbed sleep, and 5.4% had excessive sleep. After treatment, these were reduced to 12.1% and 1.6%, respectively. Similarly, only 19.9% of participants had a good appetite before treatment, which improved to 64.3% after treatment and follow-up. Irregular bowel movements were present in 34.3% of individuals enrolled in the study, and after treatment, they were reduced to 8.5%. (Fig. 5). The number of participants who presented with loose (6.3%) or hard stool (26.8%) consistency was reduced significantly after the study period, and 90.8% of participants had normal consistency at the end of the study.

During the study, a total of 37 participants dropped out. Out of these, 24 refused to continue without providing a reason, 7 had to leave as they had to go out of the station, and 3 were unwilling to provide the required blood samples. One participant declined the medicine and opted for modern management. In two more cases, it was not possible to contact the participants during the follow-up. The drug was well tolerated by most participants. There were two adverse events during the study period. One participant reported body itching and swelling at the 28th day assessment, and another reported facial swelling at the 56th day assessment. The events were mild and were managed with symptomatic treatment, and resolved without any sequelae.

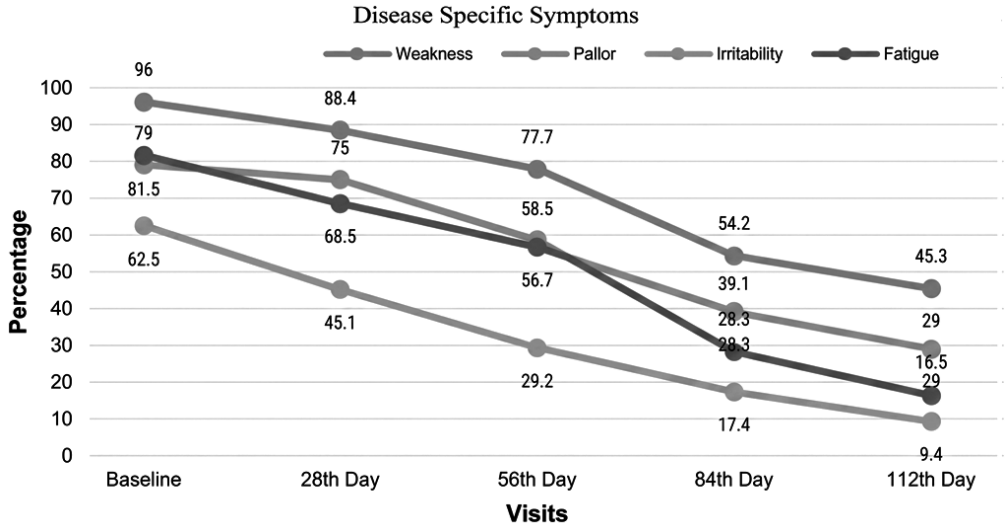

Fig. 4 — Effect of intervention on the disease-specific symptoms

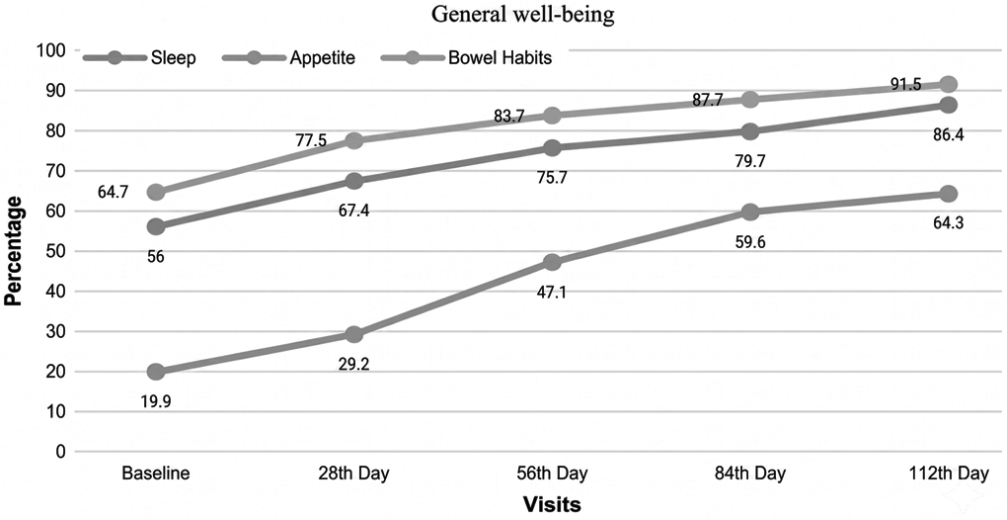

Fig. 5 — Effect of intervention on the general well-being of the participants

Discussion

In the study, the prevalence of anaemia in women was more and the majority of participants were from low socio-economic backgrounds. Lack of awareness about the need for proper nutritional requirements and social negligence towards women could be reasons for the higher frequency of the disease in females from low-income backgrounds. The data published by the WHO and other public health studies also suggest the prevalence of anaemia in low-income groups and females[4,6]. Many studies have shown that vegetarians are more likely to have lower iron stores compared to non-vegetarians leading to more anaemia cases in vegetarians[17]. In this study, the population consumes a mixed diet because of the cultural background of the community. Therefore, the observations could not be associated with dietary habits without determining the quantity and frequency of non-vegetarian food consumed by the participants. Recently, some studies have reported the association between stress and anaemia. A study conducted on rat models revealed that the study group (with induced stress with the Communication Box system) had a significant decrease in serum iron and bone marrow iron, resulting in significant inhibition of erythropoiesis compared to the control group[18].

In the present study, a significant improvement in haemoglobin was observed. Although a predefined minimally clinically important difference (MCID) for haemoglobin was not predefined, the sample size estimation was based on an expected mean increase of 0.9 g/dL, which exceeded the anticipated effect size. The improvement in haemoglobin was accompanied by a consistent reduction in disease -specific symptoms and better patient- reported outcomes related to fatigue and overall well-being. These parallel changes indicate that the observed haematological improvement is supported by meaningful clinical benefits.

Anaemia is mainly caused by nutritional deficiency, especially of the mineral iron. The reasons for this could be inadequate consumption of a healthy diet or digestive impairments. Reduced digestive capacity can result in less iron being absorbed by the body, which can induce anaemia symptoms like reduced appetite, anorexia, etc. This again results in a decrease in digestion and the absorption of minerals like iron from the food. The treatment principle in Ayurveda emphasizes the removal of *Srotorodha* (obstructive pathology occurring in channels), *Pachana* (enhancing digestion), and *Dipana* (enhancing metabolic fire) for curing the disease and further maintaining the equilibrium of *Doshas* (regulatory functional factors of the body) and *Dhatus* (major structural components of the body). *Punarnavadi Mandura* contains ingredients such as *Vidanga* (*Embelia ribes* Burm. f.), *Maricha* (*Piper nigrum* Linn.), *Haridra* (*Curcuma longa* Linn.), *Danti* (*Baliospermum montanum* Muell. Arg.), *Mustha* (*Cyperus rotundus* Linn.), *Gomutra* (Cow urine), *Chavya* (*Piper retrofractum* Vahl.) *Vibheetaki* (*Terminalia bellirica* (Gaertn.) Roxb.), *Haritaki* (*Terminalia chebula* Retz.), and *Chitraka* (*Plumbago zeylanica* Linn.) are mentioned as having *Krimihara* (anthelminthic) properties[19-23,12,24]. The studies on *Vidanga* have demonstrated its ability to promote the development of healthy gut flora ensuring the proper functioning of the whole gastrointestinal system[25]. They also help in correcting absorption abnormalities which is an important factor in nutritional deficiency diseases like anaemia. Ingredients such as *Trivrit*, *Danti*, *Haritaki* and *Vidanga* have laxative properties that will help in the elimination of undigested waste materials from the gastrointestinal tract and also ensure the proper functioning of the gastrointestinal system[26]. Ingredients like *Chitraka*, *Mustha*, *Pippalimoola*, *Chavya* and *Devadaru* are described as having digestive properties[27-29]. These will help in the digestion of undigested or partly digested food products accumulated in the body, which is the root cause of blockage in the flow of the nutritional pathway and impaired nourishment of tissues. The removal of *Ama* and opening up of *Srotas* will help in re-establishing the flow of nutrients from the alimentary tract to successive tissues. All these ingredients together act at the level of both *Jatharagni* (metabolic factors located in the digestive tract) and *Dhatwagni* (metabolic factors located in the *Dhatu*) and thus will ensure proper digestion and absorption of food. The improvements in parameters such as bowel habits, appetite and stool consistency also indicate proper gastrointestinal functioning after the intervention. The FACIT fatigue scale improved significantly along with the alleviation of symptoms such as weakness, dizziness, etc. Ingredients such as *Triphala* (*Haritaki*, *Vibheetaki*, *Amalaki*), *Pippali*, etc. are described as *Rasayana* (Rejuvenative) which helps to relieve fatigue and improve the quality of life along with alleviation of symptoms[30,31].

Cow urine contains approximately 5000 natural peptides that contribute to various bioactivities. The most abundant amino acids found in these peptides

are glycine, serine, alanine, leucine, and proline, which together make up roughly 50% of all residues present in urinary peptides[32]. A previous study has demonstrated increased bioavailability of *Mandura bhasma* when administered with cow urine[33]. The drugs *Punarnava* (*B. diffusa*), *Haridra* (*C. longa*), *Ardraka* (*Z. officinale*), etc., also contain many amino acids, including glycine[34-36]. Glycine plays a major role in heme synthesis by helping in the condensation of succinyl-CoA in mitochondria[37]. Other amino acids such as Leucine, Alanine, proline, etc. are also found to be helpful in haemoglobin synthesis[38]. *Mandura Bhasma* is rich in iron minerals and provides oral iron supplementation, an essential part of iron-deficiency anaemia. It is rich in iron and is described as the best among Ayurvedic drugs with hematinic properties[39]. The preclinical studies have also demonstrated the same effects with a significant increase in Hb and RBC-related parameters[40,13]. The presence of *Amalaki* (*E. officinalis*), which is rich in vitamin C, helps enhance the absorption of iron from the gut. Vitamin C forms a chelate with ferric iron in acidic pH in the stomach, which is soluble in the alkaline pH of the duodenum[41]. This enhances the absorption of iron from the gut, which is a main ingredient in the process of haemoglobin synthesis. Preclinical studies suggest improvements in haemoglobin and red blood cell parameters; however, these findings are presented only to explain the probable mode of action of the drug, and may not directly translate to human outcomes

When the ingredients are analysed based on modern pharmacological aspects, most of the drugs have proven carminative, appetizer, anti-oxidant and laxative properties. *Triphala* has anti-inflammatory, antioxidant, and enter protective activities and promotes gut microbiota[30]. It has been demonstrated that components like *Gomutra*, piperine in *Pippali*, and *Maricha* have bioavailability-enhancing properties that might be helpful in the absorption and continued distribution of iron, active phytoconstituents, and minerals throughout the body tissues[42,43]. The ingredients in *Punarnavadi Mandura* have demonstrated immunomodulatory and antioxidant activities in the body[15]. All these properties help in the alleviation of the associated complaints of anaemia and improve their quality of life.

Most participants completed the study. Two adverse events were reported, both of which resolved with appropriate symptomatic management. This suggests that the medication was well tolerated by participants.

Limitation of study

This study was a single-arm open-label trial conducted in a community-based setting. Hence, a comparison with other iron supplements or control group was not done. In the present study, the inclusion criteria were restricted to participants with haemoglobin levels of 8-10 g/dL. Therefore, the findings may not be generalizable to all types of anaemia. 94.6% of the participants were females, which may be due to male members not being available in community settings, as they are the earning members of the family. As the study was conducted as part of the public health program, most participants were enrolled through screening at medical camps and outreach OPDs. Limited access to laboratory facilities in community settings along with logistical constraints, restricted assessment of additional haematological parameters, including haematocrit, Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), Serum Ferritin, Serum Iron, and Total Iron Binding Capacity (TIBC). Inclusion of these parameters in the study could have provided more comprehensive insights into the effectiveness and mode of action of the study drugs. Additionally, diet-related factors were not documented in the study, which may have influenced the outcomes of the study.

Future scope

A randomized control study can be designed to validate the results with a longer follow-up period without intervention, including detailed haematological investigations.

Conclusion

The study findings suggest potential benefits of *Punarnavadi Mandura* in managing anaemia. The treatment was well tolerated, and the results indicate its potential utility in community- based settings; however, further controlled studies are needed to confirm these findings.

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Author Contributions

DM, SM, and NS were involved in the conceptualisation, design, and coordination of the study. AM drafted the manuscript, DM and SM reviewed and DM finalised the draft. AT and AS have contributed to the sample size calculation and statistical analysis of the data. ASS, GB, KS, LWB, PGN, RE, SJ, SKV, STP & TC were the principal investigators of the study. DD, IS, KG, MPP, KPD, PPN, SD, SL, SS, SUS & VT were the co-investigators of the study.

Conflicts of Interest

There are no conflicts of interest in this study.

Ethical Approval

The study was conducted in accordance with the ethical principles outlined in the ICMR ethical guidelines for human participants (2006), which are consistent with the Indian/ICH Good Clinical Practice guidelines and the Good Clinical Practice guidelines for Clinical Trials in Ayurveda, Siddha and Unani Medicine (GCP-ASU), 2013. The research proposal was approved by the Institutional Ethical Committees at each institute and recruitment was started after registering in the Clinical Trial Registry –India (CTRI/2021/07/034967 dated 19/07/2021). There were no protocol deviations or amendments during the study.

Informed Consent

The study procedure was well explained to participants verbally and in writing in their local language, and written informed consent was obtained before enrolling in the study.

Use of Artificial Intelligence (AI)

We would like to declare that no generative AI tools were used in the preparation of the scientific content, data analysis, interpretation of results, or conclusion. AI assisted tool was used solely for minor language editing for enhancement of readability of the manuscript.

Data Availability

The authors confirm that the data supporting the findings of the study are included within the article.

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