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Original Article

Randomized, Multicentric Parallel-Group Clinical Trial of the Herbo-Mineral Formulation T-AYU-HM Premium in Patients with Sickle Cell Anemia: A Prospective Study

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ABSTRACT

Background: Sickle Cell Anemia (SCA) is a hereditary blood disorder that significantly impacts the quality of life of those affected. While conventional treatments do have improved patient outcomes, they frequently fall short of managing all the symptoms and complications related to the disease. The trial was supported by established preclinical research, observational case studies and series reports on T-AYU-HM Premium. The present study is randomized, multicentric parallel-group clinical trial of the herbo-mineral formulation T-AYU-HM premium in patients with sickle cell anemia. **Materials and Methods:** The study was designed as an open-label, randomized, multicentric trial involving 100 sickle cell anemia patients (HbSS). Prior to participation, informed consent was obtained from each patient or their guardian in accordance with the ICH-GCP guideline. Data collection focused on hemoglobin variants, hematological parameters and patients' vital and clinical data, all screened based on specific inclusion and exclusion criteria. The study was conducted over a period of 180 days. The HRQOL-26 assessment tool was employed to assess the effectiveness of the treatment on patients' quality of life. **Results:** After 180 days, T-AYU-HM Premium significantly reduced sickle hemoglobin and increased fetal hemoglobin. The formulation also substantially decreased white blood cells, thereby preventing inflammation-associated complications. 93.9% consistently reported experiencing satisfactory sleep and no issues with anxiety, anger, or reduced activity. Additionally, 100% of participants reported no sudden or debilitating pain episodes and remained pain-free during the treatment period with T-AYU-HM Premium. **Conclusion:** The treatment with T-AYU-HM Premium in sickle cell disease patients demonstrated its effectiveness. Over the 180-day period, no adverse responses were reported, highlighting its safety. Furthermore, the therapy contributed to significant improvements in mental health and pain-related quality of life for the participants.

Keywords: Sickle cell disease, Fetal Haemoglobin, Red blood corpuscles, White blood cells, Blood transfusion.

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INTRODUCTION

Sickle cell anemia is characterized by the production of abnormal Hemoglobin (HbS), causing RBCs to become crescent-shaped (Centers for Disease Control and Prevention, 2024). Substantial progress has been achieved, yet the exact mechanisms underlying the complications of Sickle Cell Anemia (SCA) are not fully understood, creating a gap in targeted therapy development (Rees, Williams, and Gladwin, 2010, p. 2020). Globally, sickle cell anemia is distributed unevenly, with Low- and Middle-Income (LMIC) and high-income nations experiencing markedly different management outcomes (Thomson *et al.*, 2023). Socioeconomic limitations, awareness levels and differences in healthcare infrastructure are the main causes of these disparities (Odame, 2022). SCA presents a wide range of symptoms and complications (e.g., pain crises and organ damage), making it challenging to create standardized treatment protocols that effectively address all aspects of the disease. Many newer therapies, including gene therapies, lack long-term safety and efficacy data, pivotal for understanding their impact over time (Thompson *et al.*, 2018). Healthcare providers may have limited knowledge about sickle cell disease management, leading to inadequate treatment and support for patients (Yawn *et al.*, 2014). Existing management strategies often do not adequately address long-term complications of SCA, such as organ damage and stroke, leaving patients at risk for serious health issues. Many treatment approaches focus primarily on acute management

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rather than holistic, multidisciplinary care that address the physical, psychological and social aspects of the disease (Kato *et al.*, 2018; Das *et al.*, 2023; Ware *et al.*, 2017; Hassell, 2010).

The main problem in sickle cell patients is sickling, which can be caused by different factors, including hemolysis, cellular hyper-adhesion, oxidative stress, sterile inflammation, endothelial dysfunction, hemostatic activation and blood hyper-viscosity (National Heart, Lung and Blood Institute, 2024). Patients with sickle cell disease become hypercoagulable in an emergency because of this (Whelihan *et al.*, 2014). Preventing the polymerization of sickle hemoglobin inside red blood corpuscles under the influence of the factors mentioned above becomes critical to avert further sickling-induced vaso-occlusive complications and organ damage. Therefore, the interaction between fetal hemoglobin and sickle hemoglobin inside red blood corpuscles is crucial in determining the clinical course of sickle cell disease. Increased fetal hemoglobin levels can help alleviate the severity of sickling and efforts to boost fetal hemoglobin production are an important area of treatment and research. The actual benefit of fetal hemoglobin is its high oxygen affinities; alongside sickle hemoglobin, it prevents polymerization (Patel *et al.*, 2022). In India, HRQOL evaluation is increasingly recognized, but the psychological spectrums of participants while answering the questionnaire still require more patient-centric awareness prior to any enrollment. There are very limited alternative systems of medicine in the context of sickle cell research and rigorous research to evaluate the safety and efficacy of herbo-mineral formulations, particularly for serious or incurable diseases. Community outreach and NGO-based awareness: the government support system is at an advanced level, but still the patients' awareness towards their healthcare needs more education. Therefore, in addition to the importance of proper cleanliness, hydration and knowledge, better and more inexpensive treatment alternatives should be highlighted for sickle cell trait and sickle cell disease patients to improve their quality of life (Yawn *et al.*, 2014). T-AYU-HM Premium is a herbo-mineral formulation mentioned in Table 1 with established *in vitro* and *in vivo* preclinical studies, documented case reports, case series and CTRI-registered observational studies for sickle cell trait and sickle cell disease patients (Desai, *et al.*, 2018, Desai, *et al.*, 2022). The main research gaps in Sickle Cell Anemia (SCA) for conducting polyherbal clinical trials include the insufficient number of high-quality studies, with many existing trials being small-scale and lacking consistency. There is also a lack of standardization in herbal formulations, which complicates the comparison of results. Additionally, the safety profile and toxicity of polyherbal treatments remain underexplored, especially concerning long-term use and interactions with conventional therapies. Moreover, there is a need to bridge traditional knowledge with scientific validation to support the use of ethnobotanical treatments. Lastly, while some studies show short-term benefits, the long-term efficacy of polyherbal therapies for managing chronic SCA complications remains uncertain. Establishing standardized dosages and formulations can help minimize risks and ensure consistency in treatment. The Primary objectives of the proposed study (i) mean change in level of red blood corpuscles in participants, (ii) mean change in the level of variants of hemoglobin in participants, (iii) mean change in various blood counts in participants and (iv) mean change in major and minor complaints in participants and change in the quality of life by using a modified and validated quality of life questionnaire.

MATERIALS AND METHODS

Study approval and registration: The 180-day study was approved by the independent ethics committee of Divya Jyoti Trust, Tejas Eye Hospital and successfully registered with the Clinical Trials Registry of India (CTRI), with the assigned number CTRI/2022/06/043247 (trial registered prospectively). The trial adhered strictly to ICH-GCP guidelines, the Declaration of Helsinki and the protocol submitted for approval.

Study sites

The study sites included Dhanvantari Clinic, Ayurvedic Healthcare and Research Centre in Vyara and Bardoli, with approved principal investigators at both locations.

Study design

A randomized, multicentric, parallel-group study was conducted to evaluate the effectiveness of the herbo-mineral formulation T-AYU-HM Premium in patients with sickle cell anemia. In the conventional RCT model, the efficacy of a drug is often evaluated before assessing effectiveness; this method is now under scrutiny and is considered unethical because it can lead to a situation where a drug's benefits under controlled conditions may not translate to actual patient outcomes in real-world settings. On the contrary, in Ayurveda, patients are already using the treatments and therefore real-world effectiveness studies can be done first to further guide the necessity of studying the efficacy of specific components.

Study Intervention and population

T-AYU-HM Premium 300 mg two tablet orally twice a day with water and Folic acid 5 mg tablet once a day orally with water for sickle cell anemia participants (HbSS). Folic acid is considered as a treatment arm as standard in comparison to T-AYU-HM Premium. The rationale for selection of the standard drug treatment is that it is commonly practiced in the local region and it was previously used in randomized clinical trials in sickle cell anemia (Rabb *et al.*, 1983, Williams *et al.*, 2020).

Study period and observation timeline

Throughout the 180-day trial period, various clinical and pathological markers were assessed at baseline and subsequently on days 15, 120 and 180 of the study.

All the adverse events reported by the patients or observed by the principal investigator were documented. Informed consent and assent (if required) were received from participants prior to their inclusion in the study.

Inclusion criteria

Participants eligible for the study must be between the ages of 7 and 55 years, of both sexes and diagnosed with Homozygous Sickle cell disease (HbSS), confirmed through High-Performance Liquid Chromatography (HPLC), a microscopic sickle cell test, or a sickle cell solubility test. Written informed consent must be obtained from the parent(s) or guardian(s) for participants under 18 years of age, along with assent from participants aged 7 years and older, in accordance with ICH guidelines. Participants and their guardians must agree to adhere to the treatment guidelines and study protocol. Participants must be willing to sign the informed written consent and comply with all scheduled visits.

Additionally, participants must not have any existing or confounding medical conditions that could interfere with the study. A negative Hepatitis B test result is required for all participants. During the screening phase, participants' hemoglobin levels must be between 6.0 g/dL and 11.0 g/dL. Participants and their guardians must be willing to provide regular feedback and complete questionnaires during scheduled visits. Participants can follow either a vegetarian or non-vegetarian diet during the study.

Furthermore, participants must agree not to participate in any other clinical studies within 30 days after the last administration of the study treatment. Finally, participants must be willing to be admitted to an ambulatory site for the treatment of Vaso-Occlusive Crises (VOC) requiring pain medication.

Exclusion criteria

Participants will be excluded from the study if they are unwilling to participate or unable to attend scheduled follow-up visits at the clinic. Any condition that, in the opinion of the principal investigator, may compromise the safety of the participant or the integrity of the study will also result in exclusion. Pregnant or lactating women are excluded, as are participants with unresolved infections or existing comorbidities that may interfere with the study outcomes. Participants who have received any treatment within 7 days prior to the first dose of the study drug or who have not fully recovered from the side effects of such treatments will be excluded. Additionally, participants who have a history of hospitalization or blood transfusion within 15 days before screening are not eligible for inclusion. Those who have taken any drug other than the investigational drug in the last 7 days, or who have known allergies or hypersensitivity reactions to herbal supplements or medications will also be excluded. Participants who are unable to take and absorb oral medications or who cannot swallow tablets are not eligible. Lastly, participants who cannot understand or comply with the study instructions and requirements will be excluded from the study.

Method of Randomization

Implementing computer-generated randomization is essential for maintaining a clinical trial's integrity. Guaranteeing that the treatment groups are equivalent contributes to the validity of the results and permits an equitable evaluation of the herbo-mineral formulation's effectiveness. To avoid selection bias, keep the randomization sequence hidden from those enrolling participants until the assignment is made in sealed envelopes.

Data collection and storage

Patients asked for hematological report during baseline and sub sequential visits from designated pathologist. All the relevant data, like the informed consent, case report form and patients' vitals, clinical and pathological data, were well maintained. Data were entered into Excel spreadsheets and all the analyses were done using a Statistical Package for the Social Sciences (SPSS).

Study parameters

During baseline and follow-up visit CBC, hemoglobin variants were analysed. Headache (Shirashool), abdominal colic (Udarshool), backache (Katishool) and body ache (Angamarda) are monitored through a pain scale, whereas general weakness (Durbalaya), jaundice (Kamala) and splenomegaly (Plihodar) are more clinical signs than direct pain experiences and wouldn't typically be measured with a pain scale, so the principal investigator classifies them into grades based on mild, moderate and severe. Both fatigue and appetite can be evaluated in HRQOL-26 (Hindi version). For routine analysis of patients experiencing excruciating pain crises, the physician's own observational pain score scale was used. The study recorded dropout rates and analyzed their impact on the efficacy outcomes.

RESULTS

Study population

A total of 100 participants (N=100) were enrolled in the study. Of these, 12% of participants in the folic acid group and 4% in the T-AYU-HM Premium group dropped out (Figure 1). The participants were aged between 7 and 23 years, with the mean age being 23 years in the folic acid group and 20.90 years in the T-AYU-HM Premium group. Gender distribution was balanced across both groups, with 54% of participants being female in both groups.

Hemoglobin (Hb) and Red Blood Corpuscles (RBC) counts

After 180 days of treatment, the mean Hemoglobin (Hb) levels in the folic acid group showed an insignificant change from baseline, whereas the T-AYU-HM Premium group exhibited a statistically significant increase in Hb levels (Table 2). Specifically, the mean increase in Hb in the T-AYU-HM Premium group was observed to be higher than in the folic acid group, indicating a better response to the T-AYU-HM Premium formulation. Additionally, the Red Blood Cell (RBC) count in the T-AYU-HM Premium group remained stable, whereas a slight, though insignificant, decline in RBC counts was seen in the folic acid group. This decline in RBC count in the folic acid group can be attributed to factors such as hemolysis and sickling-induced complications, which are common in Sickle Cell Anemia (SCA) (Xu and Thein, 2022).

Hemoglobin variants

A key aspect of SCA treatment is the modulation of hemoglobin variants, particularly the reduction of sickle Hemoglobin (HbS) and the promotion of fetal Hemoglobin (HbF). In this study, T-AYU-HM Premium led to a statistically significant reduction in HbS levels and a marked increase in HbF levels, as shown in Table 3. This is a critical finding, as HbF has a higher oxygen affinity than HbA and its presence in RBCs is known to improve oxygen delivery and alleviate symptoms of SCA (Akinsheye *et al.*, 2011; Rhodes *et al.*, 2022). The ability of T-AYU-HM Premium to induce HbF production is consistent with the therapeutic goal of increasing HbF levels to reduce the clinical manifestations of SCA. In contrast, folic acid showed no significant effect on either HbS reduction or HbF induction, underscoring the limitations of folic acid in addressing the pathophysiology of SCA.

Packed Cell Volume (PCV)

The mean Packed Cell Volume (PCV), a measure of the proportion of blood volume occupied by red blood cells, showed a significant increase in the T-AYU-HM Premium group compared to baseline levels (Figure 2). This suggests that T-AYU-HM Premium may help increase the RBC mass, improving oxygen transport and alleviating symptoms of anemia in SCA patients. On the other hand, the folic acid group showed no significant change in PCV, which may indicate its limited ability to enhance RBC production or combat anemia in SCA.

White Blood Cell (WBC) Count

Both treatment groups experienced a reduction in White Blood Cell (WBC) count, which is important because elevated WBC levels are associated with increased inflammation and the onset of vaso-occlusive crises in SCA (Frenette, 2002). However, the T-AYU-HM Premium group demonstrated a significantly greater reduction in WBC counts compared to the folic acid group (Figure 1). This suggests that T-AYU-HM Premium may exert anti-inflammatory effects that could potentially reduce the frequency of crises and improve overall clinical outcomes in SCA patients.

Clinical Signs

Significant improvements in clinical signs, including splenomegaly, jaundice, pallor and general weakness, were observed in the T-AYU-HM Premium group, as shown in Table 4. These findings suggest that T-AYU-HM Premium not only helps manage the hematological aspects of SCA but also improves the clinical presentation of the disease. In contrast, the folic acid group showed significant improvement in general weakness, but other clinical signs, such as splenomegaly and jaundice, remained largely unchanged. This highlights the potential of T-AYU-HM Premium to target multiple aspects of the disease and improve overall health outcomes in SCA patients.

Pain-Related Complaints

Pain is a hallmark symptom of SCA and the management of pain is crucial for improving quality of life. In this study, participants in the T-AYU-HM Premium group showed significant improvement in pain-related complaints such as headache, body

Table 1: Composition of T-AYU-HM Premium tablets.

Ingredient Name	Botanical Name	Part Used	Quantity
Abraka Bhasma	Calyx of Mica	-	25 mg
Loha Bhasma	Calyx of iron	-	12.5 mg
Haritaki	*Terminalia chebula*	Fruit	25 mg
Sunthi	*Zingiber officinale*	Rhizome	25 mg
Shatavari	*Asparagus racemosus*	Root	25 mg
Dadima	*Punica granatum*	Fruit	12.5 mg
Jaiphal	*Myristica fragrans*	Seed	25 mg
Pippali	*Piper longum*	Fruit	37.5 mg
Guduchi	*Tinospora cordifolia*	Stem	37.5 mg
Jivanti	*Leptadinia reticlata*	Root	37.5 mg

aches and backache at 120 and 180 days compared to baseline levels (Table 5). While participants in the folic acid group also reported some improvement in pain symptoms, the changes were not statistically significant. Other pain-related complaints, such as abdominal pain, giddiness, avascular necrosis pain and priapism, showed clinical improvement in both groups, though the changes were not statistically significant. This suggests that T-AYU-HM Premium may have a more pronounced effect on pain management in SCA patients, which could potentially reduce healthcare utilization related to pain crises.

Health-Related Quality of Life (HRQOL)

Health-Related Quality of Life (HRQOL) is a crucial outcome in the management of chronic diseases like SCA. In this study, HRQOL assessments revealed significantly greater improvements in physical, emotional and social dimensions of health in the T-AYU-HM Premium group compared to the folic acid group (Table 6). Participants in the T-AYU-HM Premium group reported no cancellations of plans due to pain and no difficulties in completing daily tasks or engaging in physical activities. This suggests that T-AYU-HM Premium may have a substantial impact on the functional status and overall well-being of patients with SCA. Additionally, participants in the T-AYU-HM Premium group reported improved sleep quality, reduced anxiety and better attendance at school or work, indicating that the treatment had a positive effect on psychological and social functioning (Table 7).

Effect on Appetite and Weight

Interestingly, both treatment groups did not report any significant loss of appetite or weight loss during the study. Participants in the T-AYU-HM Premium group, however, exhibited a statistically significant weight gain over the 180-day period, with the mean

Table 2: Effect of standard drug folic acid and T-AYU-HM Premium on Hb and RBC.

Parameters	Baseline (*N*=50)	Day 15 (*N*=50)	Day 120 (*N*=49)	Day 180 (*N*=44)	*p* value within group (Baseline-D180)	*p* value between group (Baseline-D180)
Folic acid group						
Hb (gm/dL)	9.94±1.68	10.09±1.69	9.86±1.87	9.96±2.05	0.709	#0.035
RBC (millions per mm^3)	4.39±0.84	4.27±0.88	4.09±0.80	4.00±0.88	*0.010	#0.002
T-AYU-HM Premium group						
Hb (gm/dL)	8.94±1.48	9.11±1.53	9.34±1.30	9.43±1.47	*0.020	#0.035
RBC (millions per mm^3)	3.73±0.79	3.73±0.76	3.79±0.70	3.92±0.84	0.093	#0.002

Data are presented in mean ⊚ SD and analyzed by using Student '*t*' Test, * stands for $p<0.05$ statistically significant within group, # stands for statistically significant between groups of folic acid and T-AYU-HM, where N stands for Number of Participants.

Table 3: Effect of folic acid and T-AYU-HM Premium on hemoglobin variants.

Parameters	Baseline (*N*=50)	Day 180 (*N*=44)	Baseline-D180	*p* value within group (Baseline-D180)	*p* value between groups (Baseline-D180)
Folic acid group					
Hb S (%)	70.63±7.89	72.34±9.39	1.25±10.48	0.433	#0.002
Hb F (%)	19.20±6.96	18.04±8.64	-1.21±8.45	0.347	#0.001
Hb A (%)	6.38±3.71	6.08±4.33	-0.18±4.62	0.797	0.443
HbA2 (%)	3.99±2.24	4.16±2.10	0.49±2.29	0.163	#0.008
Hb-unk (%)	0.19±0.38	0.10±0.22	-0.08±0.36	0.122	0.738
T-AYU-HM Premium group					
Hb S (%)	73.65±9.17	68.17±8.53	-5.28±9.35	*0.001	#0.002
Hb F (%)	16.12±7.55	22.94±6.54	6.79±9.55	*0.001	#0.001
Hb A (%)	7.19±5.92	6.22±3.83	-1.15±7.27	0.279	0.443
HbA2 (%)	3.45±1.50	2.87±0.94	-0.62±1.59	0.538	#0.008
Hb-unk(%)	0.15±0.25	0.09±0.20	-0.06±0.22	0.059	0.738

Data are presented in mean ⊚ SD and analyzed by using Student '*t*' Test, * stands for $p<0.05$ statistically significant within group, # stands for statistically significant between groups of folic acid and T-AYU-HM, where N stands for Number of Participants.

Parameters	Folic acid					T-AYU-HM Premium					P value between groups
	Baseline (N=50)	Day 15 (N=50)	Day 120 (N=49)	Day 180 (N=44)	P value	Baseline (N=50)	Day 15 (N=50)	Day 120 (N=50)	Day 180 (N=48)	P value	
WBC (per mm^3)	8676.40 ± 2792.80	8246.60 ± 3404.55	8737.76 ± 4070.99	8352.27 ± 2738.84	0.73	10554.00 ± 4258.59	9772.00 ± 3400.42	9904.40 ± 4046.06	8982.92 ± 3098.85	0.05	0.143
Platelet (Cells/ mm^3)	335880. ± 138418.86	328420. ± 122896.02	311071. ± 145018.39	347727.± 169806.64	0.49	443020.00 ± 507532.55	368300.00 ± 150368.83	334240.00 ± 127453.96	340718.75 ± 139110.66	0.17	0.130
MCHC (g/dL)	32.95 ± 1.93	32.75 ± 1.99	33.23 ± 1.96	33.31 ± 2.30	0.52	32.68 ± 1.66	32.91 ± 1.69	32.85 ± 1.48	32.61 ± 1.61	0.92	0.556
MCH (pg)	23.42 ± 4.45	23.65 ± 4.20	24.90 ± 4.78	24.91 ± 5.85	0.26	24.54 ± 4.94	24.89 ± 4.23	24.78 ± 4.18	28.45 ± 27.55	0.34	0.521
MCV (fl)	70.63 ± 11.29	71.92 ± 10.48	73.64 ± 12.51	73.13±14.29	0.47	75.65± 11.43	75.26 ± 10.08	74.95 ± 11.94	74.37 ± 10.84	0.40	0.285
PCV (%)	30.43 ± 4.92	30.70 ± 6.02	29.49 ± 5.52	30.19 ± 6.08	0.42	27.51 ± 4.63	28.38 ± 5.10	28.33 ± 4.11	29.13 ± 4.81	0.02	0.024
Neutrophil (%)	62.54 ± 9.51	62.84 ± 12.23	63.22 ± 10.95	61.68 ± 8.77	0.69	60.92± 10.67	60.60 ± 9.93	60.96 ± 10.25	61.46 ± 8.29	0.87	0.695
Eosinophil (%)	4.22 ± 1.89	4.14 ± 3.10	4.18 ± 2.56	3.68 ± 1.90	0.21	4.46 ± 2.54	4.42 ± 1.84	4.12 ± 2.06	3.81 ± 2.15	0.18	0.762
Basophil (%)	0.00 ± 0.00	0.12 ± 0.59	0.00 ± 0.00	0.00 ± 0.00	1.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.08 ± 0.58	0.34	0.342
Lymphocytes (%)	32.28 ± 9.56	32.52 ± 11.75	31.80 ± 9.71	33.32 ± 8.40	0.62	34.02± 10.38	34.22 ± 9.77	34.00 ± 9.51	34.29 ± 7.99	0.80	0.871
Monocytes (%)	0.52 ± 1.22	0.58 ± 1.84	0.57 ± 1.26	0.64 ± 1.37	0.66	0.60 ± 1.34	0.58 ± 1.47	0.74 ± 1.79	0.35 ± 0.81	0.23	0.269

Data are presented in mean ± SD and analyzed by using Student 't' Test , * stands for P<0.05 statistically significant within group, # stands for statistically significant between groups of folic acid and T-AYU-HM, where N stands for Number of Participants

Figure 2: Effect of treatment on heamotological parameters.

Table 4: Effect of treatments on clinical signs in sickle cell anemia patients.

Parameter	Time point	Folic acid	T-AYU-HM Premium	*p* value between Group
Splenomegaly (Plihodar)	Baseline	1.08±1.63	1.20±1.46	0.561
	15 Days	1.16±1.52	1.08±1.35	0.368
	120 Days	0.49±1.04	0.50±1.13	0.412
	180 Days	1.16±1.65	0.41±0.81	#0.034
Jaundice (Kamala)	Baseline	0.16±0.68	0.80±1.34	#0.039
	15 Days	0.32±1.10	0.64±1.24	0.502
	120 Days	0.08±0.40	*0.25±0.79	0.103
	180 Days	0.09±0.43	*0.29±0.82	0.07
Pallor (Panduta)	Baseline	0.28±0.99	1.20±1.34	#0.001
	15 Days	0.36±0.88	0.92±1.41	0.28
	120 Days	0.08±0.40	*0.38±0.98	#0.011
	180 Days	0.09±0.43	*0.24±0.78	#0.004
General weakness (Durbalaya)	Baseline	1.36±1.43	1.40±1.47	0.92
	15 Days	1.12±1.41	1.20±1.51	0. 920
	120 Days	*0.33±0.85	0.71±1.62	0.968
	180 Days	*0.42±0.93	*0.53±1.06	0.928

Grade: Normal (0), Mild:1-3, Moderate 4-6, Severe: 7-9, Very Severe: 10, where * $p<0.05$ within group, # p value <0.05 between group are considered significant. Data are analyzed by Wilcoxon Sign Rank Test (within group) and Mann Whitney U Test (Between Groups).

Table 5: Effect of treatment on pain related symptoms in participants.

Parameter	Time point	Folic acid	T-AYU-HM Premium	*p* value diff between
Bodyache	Baseline	1.76±1.84	1.84±1.66	0.718
	15 Days	1.52±1.59	1.64±2.05	0.976
	120 Days	0.53±1.06*	0.71±1.52*	0.459
	180 Days	0.93 ±1.33*	0.37±0.97*	0.085
Backache	Baseline	1.40 ±1.77	0.88 ±1.57	0.158
	15 Days	1.36 ±1.74	0.60 ±1.47	0.429
	120 Days	0.69 ±1.26*	0.13 ±0.64*	0.833
	180 Days	0.98 ±1.47*	0.08 ±0.57*	0.368
Abdominal pain	Baseline	0.72±1.44	0.36±0.78	0.502
	15 Days	0.64±1.54	0.40±0.81	0.787
	120 Days	0.16±0.69*	0.21±0.62	0.378
	180 Days	0.47±1.05	0.16±0.55	1.000

Grade: Normal (0), Mild:1-3, Moderate 4-6, Severe: 7-9, Very Severe: 10, where * $p<0.05$ within group, # p value <0.05 between group are consider significant. Data are analyzed by Wilcoxon Sign Rank Test (within group) and Mann Whitney U Test (between groups).

Table 6: Effectiveness responses of treatments on social health in HRQOL of participants.

Parameter	Time point	Folic acid					T-AYU-HM Premium					*p* value diff between
Social Health		N	R	S	O	A	N	R	S	O	A	
Interaction and problem solving	Baseline	50	44	6	-	-	64	32	4	-	-	
	180	*34.1	45.5	20.5	-	-	*16.3	36.7	44.9	2		#0.047

N=Never, R=Rarely, S=Sometimes, O=Often, A=always, * stands $p<0.05$ considered significant analyzed by Chi-Square test within group and # stands $p<0.05$ considered significant analyzed by Chi-Square test group.

Table 7: Response of effectiveness of treatments on mental health in HRQOL of patients.

Parameter	Time point	Folic acid (*N*=50)					T-AYU-HM Premium (*N*=50)					*p* value diff between
Mental health evaluation		N	R	S	O	A	N	R	S	O	A	
Anxiety, stress and depression	Baseline	-	80	6	14	0	8	44	46	2	-	
	180 Days		38.6	13.6	36.4	11.4	-	-	4.1	2	93.9	#0.001
Sleep	Baseline	-	80	6	14	0	8	44	46	2	-	
	180 Days		38.6	13.6	36.4	11.4			4.1	2	93.9	#0.001

Data are presented in percentage, N=Never, R=Rarely, S=Sometimes, O=Often, A=always, *stands for $p<0.05$ considered significant analyzed by Chi-Square test within the groups, #stands for $p<0.05$ considered significant analyzed by Chi-Square test between the groups.

Table 8: Effectiveness responses of treatments on physical health in HRQOL of participants.

Parameter	Time point	Folic acid (*N*=50)					T-AYU-HM Premium(*N*=50)					*p* value diff between
Physical health related evaluation		N	R	S	O	A	N	R	S	O	A	
Debilating pain and Pain attack	Baseline	16	32	26	24	2	6	22	44	26	2	
	180	*95.5	2.3	-	2.3	-	*100	-	-	-	-	0.131
Severe pain in joints/ shoulders/hip	Baseline	16	32	26	24	2	6	22	44	26	2	
	180	*22.7	31.8	22.7	22.7	-	*100	-	-	-	-	#0.001
Pain associated cancel plans	Baseline	16	32	26	24	2	6	22	44	26	2	
	180	*63.6	29.5	6.8	-	-	*100	-	-	-	-	#0.001

Data are presented in percentage, N=Never, R=Rarely, S=Sometimes, O=Often, A=always, * stands for $p<0.05$ considered significant analyzed by Chi-Square test within the groups, # stands for $p<0.05$ considered significant analyzed by Chi-Square test between the groups.

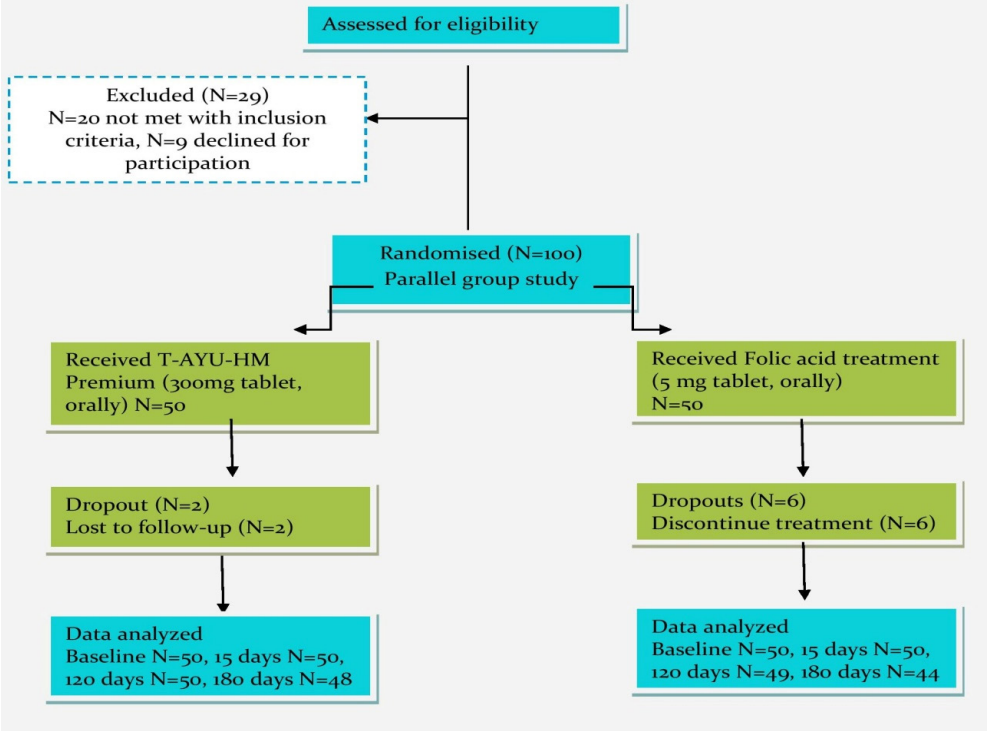

Figure 1: CONSORT flowchart for enrollment, randomization, follow-up and analysis flow diagram. Where N=Number of Participants.

weight increasing from 38.37±12.25 kg at baseline to 39.55±12.29 kg at 180 days (Table 8). This weight gain suggests that T-AYU-HM Premium may positively affect nutritional status, which is crucial for maintaining health in SCA patients, as they often struggle with malnutrition due to chronic illness.

DISCUSSION

The results of this study provide compelling evidence supporting the use of T-AYU-HM Premium as a potentially superior treatment option for Sickle Cell Anemia (SCA) compared to folic acid, particularly in terms of hematological improvements, pain management and overall, Health-Related Quality of Life (HRQOL).

One of the most notable findings from this study was the significant increase in fetal Hemoglobin (HbF) and the reduction in sickle Hemoglobin (HbS) in the T-AYU-HM Premium group. This is a critical result because increasing HbF levels is one of the primary therapeutic strategies for managing SCA. HbF has a higher oxygen affinity than adult hemoglobin and its increased production helps reduce the sickling of red blood cells, thus improving oxygen delivery and alleviating many of the symptoms of SCA (Akinsheye *et al.*, 2011; Rhodes *et al.*, 2022). In contrast, folic acid did not significantly affect either HbS or

HbF levels, which underscores its limitations in addressing the pathophysiology of SCA. The significant improvement in Packed Cell Volume (PCV) in the T-AYU-HM Premium group further supports its role in improving red blood cell mass and alleviating anemia. These hematological benefits are consistent with the therapeutic goals for SCA, where the maintenance of adequate hemoglobin levels and RBC count is crucial for reducing the risk of complications, such as stroke, organ damage and fatigue (Ershler *et al*., 2023).

Another important finding was the reduction in White Blood Cell (WBC) count in both treatment groups, with a significantly greater decrease in the T-AYU-HM Premium group. Elevated WBC levels have been linked to increased inflammation and the onset of vaso-occlusive crises in SCA patients (Frenette, 2002). The greater reduction in WBC count in the T-AYU-HM Premium group suggests that this formulation may help reduce inflammation, potentially decreasing the frequency and severity of these painful crises. Additionally, the significant improvements in clinical signs such as splenomegaly, jaundice and pallor in the T-AYU-HM Premium group, coupled with the improvement in pain-related complaints, indicate that T-AYU-HM Premium has a broad range of beneficial effects in managing the symptoms of SCA.

Sickle cell disease is associated with chronic pain, which significantly affects the patient's quality of life. The significant improvement in pain-related complaints observed in the T-AYU-HM Premium group suggests that this treatment may have a strong analgesic effect. This is supported by the significant improvements in HRQOL outcomes, where participants in the T-AYU-HM Premium group reported no pain-related restrictions on physical activity and better overall well-being compared to the folic acid group. These findings suggest that T-AYU-HM Premium could play a crucial role in enhancing the overall quality of life for SCA patients, addressing both the physical and psychological dimensions of the disease.

The increase in body weight observed in the T-AYU-HM Premium group is another important aspect of this study. Malnutrition is common in SCA patients and maintaining a healthy weight is essential for optimal health and disease management. The significant weight gain observed in the T-AYU-HM Premium group suggests that this treatment may have a positive effect on nutritional status, which could further improve patient outcomes.

The main limitation of the present trial is it was restricted with limited number of participants considering the cost of monitoring hemoglobin variant at schedule visit. The treatment with T-AYU-HM Premium demonstrated sustained improvements in hemoglobin levels and red blood cell counts. Notably, it induced a significant increase in fetal hemoglobin and a reduction in sickle hemoglobin, an effect not observed with folic acid treatment. Additionally, white blood cell counts were effectively controlled and neutrophil and lymphocyte counts remained balanced, which was not achieved with folic acid. T-AYU-HM Premium also prevented hemoglobin polymerization, leading to marked improvements in clinical symptoms compared to folic acid treatment. Desai *et al*., (2018) conducted a pilot-scale observational study comparing folic acid and T-AYU-HM Premium in 2010, with prior ethics approval and adherence to trial guidelines and regulations. Therefore, trial results are not only considered valid within the study's confines but are also applicable to the real world, considering differences in populations, settings and other contextual factors. While pain-related symptoms were resolved in both treatment groups, HRQOL assessments showed significantly greater improvements in physical, mental and social health outcomes in the T-AYU-HM Premium group compared to the folic acid group.

CONCLUSION

T-AYU-HM Premium increases fetal Hemoglobin (HbF) levels, leading to improved red blood cell function and decreased sickling. This can result in fewer symptoms related to anemia and a reduced requirement for blood transfusion. Remarkable improvements in clinical signs are suggestive of no vaso-occlusive crisis or complications. Pain scores are suggestive of reducing pain episodes and complications. A reduction in pain crises and better sickle cell disease management in turn enhance the quality of life in patients. There was no untoward reaction or effect observed or reported during the trial period, which also indicated better functioning and overall well-being. 93.9% of patients report no anxiety and depression, contributing to improved mental health. Therefore, T-AYU-HM Premium is found to be safe and effective, which can lead to reduced hospital visits, repetitive blood transfusions and consumption of painkillers for sickle cell patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SCD: Sickle cell disease; **SCA:** Sickle cell anemia; **TSH:** Thyroid-stimulating hormone; **HbF:** Fetal hemoglobin; **CRP:** C-reactive protein. **ESR:** Erythrocyte sedimentation rate; **RBC:** Red blood corpuscles; **WBC:** White blood cells; **Kgs:** Kilograms; **HRQOL:** Health-related quality of life.

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