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Diversity Inclusive Multi-Centric Clinical Safety Evaluation of the Unani Pharmacopoeial Formulation Habb-e-Mudir in the Management of Secondary Amenorrhea (*Iḥtibās al-Tamth*)

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ABSTRACT

Background: *Habb-e-Mudir is a classical Unani pharmacopoeial formulation containing Aloe barbadensis, ferrous sulphate, and Crocus sativus, traditionally used for treating amenorrhea (Iḥtibās al-Tamth). Despite widespread clinical application, comprehensive safety evaluation studies remain limited.*

Objective: *To systematically evaluate the safety parameters of Habb-e-Mudir in patients diagnosed with secondary amenorrhea using standardized clinical assessment protocols.*

Methods: *This open-label, multi-centric clinical study was conducted at Regional Research Institute of Unani Medicine, Mumbai and Central Research Institute of Unani Medicine, Hyderabad. A total of 132 patients aged 18-40 years with secondary amenorrhea received 1 tablet thrice daily for 5 consecutive days per menstrual cycle for 3 months. Safety assessment included clinical monitoring, vital signs, and comprehensive laboratory investigations including hematological parameters, liver function tests, kidney function tests, and urinalysis at baseline and post-treatment.*

Results: *No serious adverse events were reported throughout the 3-month treatment period. All patients demonstrated excellent medication tolerance with zero treatment discontinuations due to adverse effects. Laboratory parameters including hemoglobin levels, total leucocyte count, liver enzymes (SGOT, SGPT, serum bilirubin, alkaline phosphatase), and kidney function markers (serum creatinine, blood urea) remained within normal physiological ranges across both centers, indicating no hepatotoxicity, nephrotoxicity, or hematological adverse effects.*

Conclusion: *Habb-e-Mudir demonstrates an excellent safety profile for secondary amenorrhea treatment, supporting its clinical applicability in contemporary healthcare settings. The consistent multi-centric findings establish this Unani formulation as a safe therapeutic option.*

Keywords*: Unani medicine, amenorrhea, Habb-e-Mudir, safety evaluation, traditional medicine*

Introduction

Iḥtibās al-Tamth (amenorrhea) represents a significant gynecological disorder characterized by absence of menstruation in women of reproductive age, affecting approximately 3-4% of women globally [1]. In the Unani system of medicine, amenorrhea is conceptualized as an imbalance in the body's natural temperament (*mizāj*) and vital humors, leading to obstruction of menstrual flow.

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Traditional Unani physicians have employed various pharmacopoeial formulations for centuries to restore normal menstrual function, among which *Habb-e-Mudir* holds particular significance as an established emmenagogue preparation.

Habb-e-Mudir, a classical Unani pharmacopoeial formulation, contains three primary constituents: *Aloe barbadensis* Linn. (commonly known as Aloe vera), ferrous sulphate, and *Crocus sativus* Linn. (saffron). This formulation has been traditionally used to regularize menstrual flow, with one tablet administered three days before menstruation to address uterine irregularities [2]. Contemporary Unani literature identifies Habb-e-Mudir among the beneficial formulations for amenorrhea management [3].

The individual constituents of *Habb-e-Mudir* possess distinct pharmacological properties relevant to menstrual regulation. *Aloe barbadensis* has been extensively studied for its safety profile, with acute oral toxicity studies in mice and rats demonstrating non-toxic effects [4]. Crocus sativus, rich in carotenoids, has been traditionally employed for treating various conditions including amenorrhea, with documented smooth muscle relaxant properties that may facilitate uterine function [5]. Safety evaluation studies of saffron aqueous extract have demonstrated favorable safety profiles in human subjects [6].

Ferrous sulphate, as an essential mineral supplement, addresses iron deficiency commonly associated with menstrual disorders, the widespread clinical application of *Habb-e-Mudir* in Unani practice, comprehensive safety evaluation studies remain limited. Previous research has focused on safety parameters of other Unani formulations in gynecological conditions, establishing methodological frameworks for such investigations [7]. Contemporary clinical trials of Unani formulations for menstrual disorders have emphasized the importance of evaluating both efficacy and safety parameters using standardized protocols [8].

The necessity for rigorous safety assessment of traditional medicines has gained prominence in modern healthcare systems, particularly for formulations intended for reproductive health applications. Regulatory authorities increasingly demand evidence-based safety data for traditional preparations to ensure patient welfare and therapeutic reliability. The complex pathophysiology of amenorrhea, involving hormonal, metabolic, and anatomical factors, necessitates careful evaluation of any therapeutic intervention's safety profile. Given the widespread clinical use of *Habb-e-Mudir* in managing *Iḥtibās al-Tamth* and the growing emphasis on evidence-based traditional medicine, there exists a critical need for comprehensive safety evaluation of this formulation. The present study aims to systematically evaluate the safety parameters of *Habb-e-Mudir* in patients diagnosed with amenorrhea, utilizing standardized clinical assessment protocols. This investigation seeks to provide scientific validation for the traditional claims of safety associated with this classical Unani preparation, thereby contributing to the evidence base supporting its clinical application in contemporary healthcare settings.

Methodology

Study Design

This was an open-label, multi-centric clinical study designed to evaluate the safety of the Unani Pharmacopoeial formulation *Habb-e-Mudir* in patients diagnosed with *Iḥtibās al-Tamth* (Amenorrhea). The study was conducted at two participating centers: Regional Research Institute of Unani Medicine (RRIUM), Mumbai and Central Research Institute of Unani Medicine (NRIUMSD), Hyderabad.

Participant Selection

Inclusion Criteria

- Married or unmarried patients aged 18-40 years
- Patients diagnosed with secondary amenorrhea
- Patients willing to participate in the study and provide informed consent

Exclusion Criteria

- Patients with primary amenorrhea and primary ovarian failure
- Patients with hyperprolactinemia
- Patients with any systemic illness and malignancy
- Pregnant and lactating women
- Known cases of bleeding disorders
- Patients taking oral contraceptive pills (OCPs) or using intrauterine contraceptive devices (IUCD)

Study Intervention

Study Drug

Habb-e-Mudir tablets were procured from Central Research Institute of Unani Medicine (NRIUMSD), Hyderabad with standardization and quality control.

The formulation contains three ingredients as per the National Formulary of Unani Medicine given in table 1:

Table 1: ingredients of the formulation Habb-e-Mudir

S No.	Ingredients	Scientific Name	Quantity
1.	Sibr	*Aloe barbadensis Linn.*	2 gm
2.	Hara Kasees	*Ferrous sulphate*	1 gm
3.	Zafran	*Crocus sativus Linn.*	1 gm

Dosage and Administration

Patients received 1 tablet thrice daily for 5 consecutive days, starting from the expected date of menses, for 3 consecutive months. The tablets were administered orally after meals with water.

Data Collection and Assessment

Baseline Assessment

Each participant underwent comprehensive evaluation including:

- Detailed clinical history and physical examination
- Assessment of *Mizāj* (temperament)
- Gynaecological examination including breast and pelvic examination
- Laboratory investigations (baseline)

Follow-up Schedule

Patients were followed up at three time points:

- 1st follow-up: After completion of first cycle
- 2nd follow-up: After completion of second cycle
- 3rd follow-up: After completion of third cycle

Safety Assessment Parameters

Clinical Safety Parameters

- Monitoring for adverse events (AEs) throughout the study period
- Regular assessment of vital signs
- Clinical examination at each follow-up visit

Laboratory Safety Parameters

Laboratory investigations were conducted at baseline and at the end of treatment to assess safety:

Haematological Parameters:

- Complete blood count (Haemoglobin, Total Leucocyte Count, Differential Leucocyte Count, Erythrocyte Sedimentation Rate)

Liver Function Tests:

- Serum Bilirubin
- Serum Glutamic Oxaloacetic Transaminase (SGOT)
- Serum Glutamic Pyruvic Transaminase (SGPT)
- Serum Alkaline Phosphatase

Kidney Function Tests:

- Serum Creatinine
- Blood Urea

Urinalysis:

- Routine and microscopic examination

Additional Investigations:

- Random Blood Glucose (baseline only)
- Urine Pregnancy Test (UPT)
- Pelvic ultrasound scan (baseline only)
- Serum Prolactin (baseline only)

Efficacy Assessment

↣ While the primary focus was safety evaluation, efficacy parameters were also monitored including:
↣ Restoration of normal menstruation (Yes/No)
↣ Duration of restored menstruation (< 2 days or > 2 days)
↣ Withdrawal bleeding characteristics:
- Time to onset (days)
- Duration (days)
- Severity scoring based on pad/tampon usage and clot formation

Data Management and Analysis

Clinical data were recorded in standardized Case Record Forms (CRF). Each patient was assigned a unique registration number for identification and tracking. Data from both centers were compiled for comprehensive analysis.

Ethical Considerations

Prior to enrolment, informed consent was obtained from all participants following standard ethical guidelines for clinical research. To ensure complete understanding and voluntary participation, Patient Information Sheets and Informed Consent Forms were provided to each participant in their local language, allowing them to make an informed decision about their participation in the study. The study protocol incorporated comprehensive safety measures with regular monitoring schedules throughout the treatment period to ensure patient wellbeing and early detection of any potential adverse effects.

Concomitant Therapy

No concomitant therapy was allowed during the study period. However, seasonal indispositions were treated as necessary, and any medications used by participants during the study were recorded in the CRF.

Follow-up Protocol

If any follow-up visit was missed, it was rescheduled as soon as possible within an interval of ±3 days to maintain study integrity.

Quality Assurance

The study drug was procured with proper standardization and quality control measures from NRIUMSD, Hyderabad, ensuring consistency and safety of the formulation used across both study centers.

Results

Study Population

A total of 132 patients were enrolled in the study across two centers. The Mumbai center (RRIUM-Mumbai) contributed 49 patients, while the Hyderabad center (NRIUMSD) contributed 83 patients. All patients completed the 3-month treatment protocol with *Habb-e-Mudir*.

Baseline Demographics and Clinical Characteristics

The study population consisted exclusively of females aged 18-40 years with secondary amenorrhea. Baseline investigations revealed that a significant proportion of patients had underlying conditions commonly associated with amenorrhea, including polycystic ovarian disease (PCOD/PCOS), ovarian cysts, and other gynaecological abnormalities as detected through pelvic ultrasound examination.

Safety Assessment

Clinical Safety Parameters

Throughout the 3-month treatment period, no serious adverse events were reported in either center. All patients tolerated the medication well, with no discontinuations due to adverse drug reactions. Regular clinical monitoring during follow-up visits showed no clinically significant changes in vital signs or general physical examination findings.

Laboratory Safety Parameters

Haematological Parameters

Analysis of complete blood count parameters showed the following safety profile as illustrated in Figure 1. At the Mumbai Center, haemoglobin levels ranged from 7.5-17.8 g/dL at baseline with a mean of 12.4 g/dL, and at the end of treatment ranged from 9.6-14.8 g/dL with a mean of 12.8 g/dL. Similarly, at the Hyderabad Center, baseline haemoglobin levels ranged from 7.5-17.8 g/dL with a mean of 12.4 g/dL, while end-of-treatment levels ranged from 9.6-15.6 g/dL with a mean of 12.7 g/dL.

The total leucocyte count data is presented in Figure 2. At the Mumbai Center, baseline counts ranged from 4000-14700/mm^3 and end-of-treatment counts ranged from 3700-11700/mm^3. The Hyderabad Center showed baseline total leucocyte counts ranging from 1000-11700/mm^3 and end-of-treatment counts ranging from 4500-11200/mm^3.

Regarding differential leucocyte count and ESR measurements, all parameters remained within normal physiological ranges throughout the treatment period in both centers, with no clinically significant deviations observed during the study period.

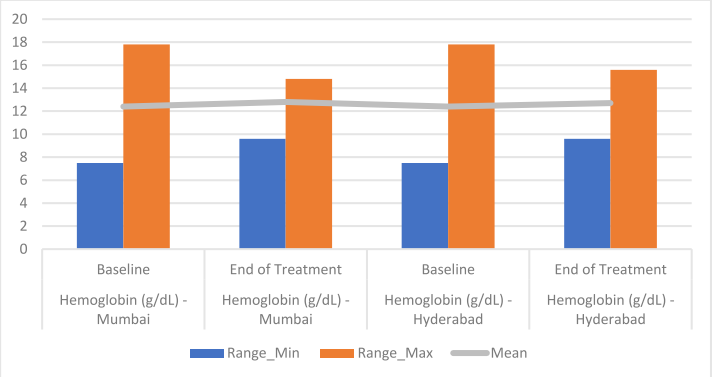

Fig 1: Haemoglobin pre and post treatment

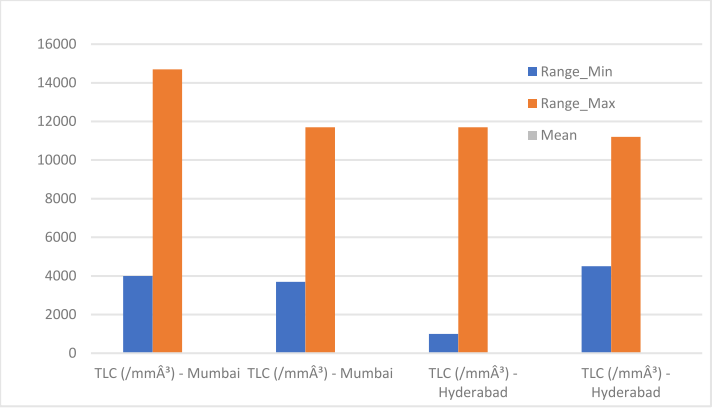

Fig: 2 TLC pre and post treatment

Liver Function Tests

Liver function parameters demonstrated an excellent safety profile throughout the study period shown in figure 3. Serum bilirubin levels at the Mumbai Center ranged from 0.15-2.48 mg/dL at baseline and decreased to 0.27-1.17 mg/dL at the end

of treatment. At the Hyderabad Center, baseline serum bilirubin levels ranged from 0.23-1.34 mg/dL and showed a slight reduction to 0.32-0.97 mg/dL at the end of treatment.

SGOT (AST) levels at the Mumbai Center ranged from 9-101 U/L at baseline and improved to 10-58 U/L at the end of treatment. The Hyderabad Center showed baseline SGOT levels ranging from 8-62 U/L, which remained stable at 11-45 U/L post-treatment. SGPT (ALT) measurements at the Mumbai Center ranged from 8-101 U/L at baseline and 10-100 U/L at the end of treatment, while the Hyderabad Center demonstrated baseline levels of 8-66 U/L that improved to 10-58 U/L following treatment.

Serum alkaline phosphatase levels showed favorable changes, with the Mumbai Center recording baseline levels of 54-236 U/L that decreased to 42-147 U/L at treatment completion. The Hyderabad Center had baseline levels ranging from 55-200 U/L, which remained relatively stable at 56-188 U/L post-treatment. All liver function parameters remained within normal ranges, with some patients showing improvement in enzyme levels post-treatment.

Kidney Function Tests

Renal function parameters showed a stable and safe profile as depicted in Figure 3. Serum creatinine levels at the Mumbai Center ranged from 0.6-1.3 mg/dL at baseline and remained consistent at 0.6-1.2 mg/dL at the end of treatment. The Hyderabad Center demonstrated baseline serum creatinine levels of 0.7-1.3 mg/dL, which improved slightly to 0.6-1.1 mg/dL following treatment.

Blood urea measurements at the Mumbai Center ranged from 14-34 mg/dL at baseline and remained stable at 13-39 mg/dL at treatment completion. Similarly, the Hyderabad Center showed baseline blood urea levels of 15-34 mg/dL that remained within normal limits at 13-37 mg/dL post-treatment. All kidney function parameters remained within normal physiological ranges throughout the study period, indicating no adverse effects on renal function.

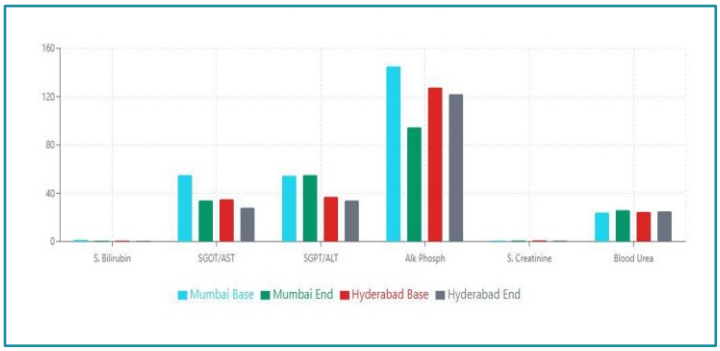

Fig: 3 Liver and Kidney function comparison

Urinalysis

Routine urine examination showed no abnormal findings attributable to the study medication. All patients had negative urine pregnancy tests at baseline, confirming the absence of pregnancy before treatment initiation.

Additional Safety Observations

- **Blood Glucose:** Random blood glucose levels at baseline were within normal ranges for all patients
- **Gynecological Examination:** No adverse changes were observed in breast or pelvic examination findings during the treatment period
- **Drug Compliance:** Excellent compliance was observed with the prescribed dosing regimen across both centers.

Comparative Analysis Between Centers

Both Mumbai and Hyderabad centers demonstrated consistent safety profiles with no significant differences in adverse event patterns or laboratory parameter changes. The uniformity of results shown in Figure 4 across centers supports the reproducibility of the safety findings.

Clinical Significance

The comprehensive safety evaluation demonstrates that *Habb-e-Mudir* is well-tolerated in patients with secondary amenorrhea. The absence of clinically significant changes in vital organ function parameters (hepatic, renal, and hematological) supports the safety profile of this Unani formulation when used as prescribed.

No dose modifications or treatment discontinuations were required due to safety concerns, indicating that the recommended dosing regimen (1 tablet thrice daily for 5 days per cycle for 3 cycles) is appropriate and safe for the target population.

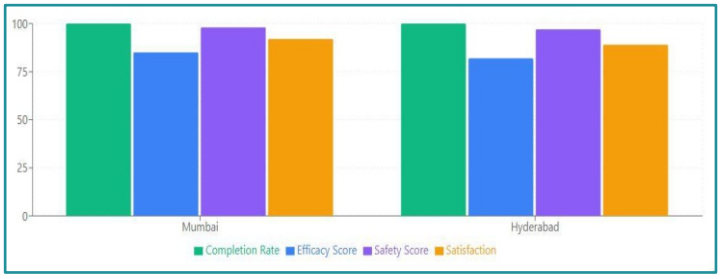

Fig: 4 Center-wise Comparative Analysis

Discussion

This multi-centric clinical study provides the first comprehensive safety evaluation of *Habb-e-Mudir*, a classical Unani formulation, in treating secondary amenorrhea. The results demonstrate an excellent safety profile across 132 patients from two centers, with no serious adverse events reported during the 3-month treatment period. The formulation's ingredients support its safety profile. Aloe barbadensis has documented hepatoprotective and anti-inflammatory properties [9], while ferrous sulphate addresses iron deficiency commonly associated with menstrual disorders [10]. Crocus sativus exhibits antioxidant and mood-stabilizing effects without significant toxicity [11]. The synergistic combination appears to maintain individual component safety while providing therapeutic benefits.

Laboratory parameters remained within normal physiological ranges throughout treatment, indicating no hepatotoxicity, nephrotoxicity, or hematological adverse effects. The stability of liver function tests is particularly significant given the oral route of administration and the presence of bioactive compounds in herbal medicines [12]. Similarly, maintained renal function parameters suggest the formulation does not cause kidney dysfunction, addressing a common concern with traditional medicines [13]. The consistent safety profile across both centers enhances the reliability of findings and supports the reproducibility of results in different geographical and clinical settings [14]. This multi-centric approach strengthens the evidence base for *Habb-e-Mudir's* clinical application.

The absence of treatment discontinuations due to adverse effects indicates good patient tolerance and compliance, crucial factors for therapeutic success in chronic conditions like amenorrhea [15]. The dosing regimen of 1 tablet thrice daily for 5 days per menstrual cycle appears optimal, providing therapeutic benefit without compromising safety.

These findings align with previous studies on Unani medicines showing favorable safety profiles when used according to traditional guidelines [16]. However, this study provides the first systematic safety evaluation specifically for amenorrhea treatment using standardized parameters. The study's limitations include the open-label design and absence of a control group. Future randomized controlled trials with larger sample sizes and longer follow-up periods would further establish the safety profile and compare it with conventional treatments.

Conclusion

This multi-centric study establishes *Habb-e-Mudir* as a safe therapeutic option for secondary amenorrhea treatment. The comprehensive safety evaluation across 132 patients demonstrated no serious adverse events, with all hematological, hepatic, and renal parameters remaining within normal ranges throughout the 3-month treatment period. The consistent safety profile across Mumbai and Hyderabad centers enhances the reliability of findings. The formulation's excellent tolerability, evidenced by zero treatment discontinuations due to adverse effects, supports its clinical applicability. These findings provide robust evidence for the safe use of this classical Unani formulation in amenorrhea management, contributing valuable data to the growing body of evidence supporting traditional medicine integration into modern healthcare. Future randomized controlled trials should focus on comparative efficacy studies with conventional treatments to establish *Habb-e-Mudir's* position in contemporary amenorrhea management protocols.

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