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Clinical validation of the unani pharmacopoeial formulation Habb-e-Mudir for the treatment of secondary amenorrhea (Iḥtibās al-tamth): A multicentric open-label study

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Abstract
Objective: To validate the efficacy of Unani pharmacopoeial formulation *Habb-e-Mudir* in patients with Iḥtibās al-Tamth (amenorrhea).
Methods: An open-label, multi-centric clinical trial was conducted at RRIUM Mumbai and NRIUMSD Hyderabad, enrolling 132 patients with secondary amenorrhea aged 18-40 years. Participants received *Habb-e-Mudir* tablets (containing Aloe barbadensis 2gm, Ferrous sulphate 1gm, and Crocus sativus 1gm) three times daily for 5 consecutive days from expected menses date, continued for 3 months. Primary endpoints included restoration of normal menstruation and withdrawal bleeding assessment parameters.
Results: Complete efficacy data from Mumbai center (n=49) demonstrated progressive menstrual restoration: 89.8% after first cycle, 100% after second cycle, and sustained response in 95.9% at final assessment. Duration of menstrual flow significantly improved from baseline 1.8±0.6 days to 3.8±1.2 days (111% increase). Severity scoring showed 68.4±24.7% mean improvement. Treatment response classification revealed complete relief in 57.1%, partial relief in 38.8%, and treatment failure in only 4.1%. Safety assessment across all 132 patients showed zero adverse events with normal post-treatment laboratory parameters.
Conclusion: *Habb-e-Mudir* demonstrated excellent therapeutic efficacy (95.9% success rate) and safety profile in treating secondary amenorrhea, supporting its integration into evidence-based gynecological practice within the Unani system of medicine.

Keywords: Habb-e-mudir, amenorrhea, unani medicine, emmenagogue, clinical validation

Introduction

Amenorrhea, defined as the absence of menstruation in women of reproductive age, represents a significant gynecological concern affecting 3-4% of women globally and requiring comprehensive evaluation when primary amenorrhea persists beyond 15 years of age or secondary amenorrhea occurs for three consecutive months in previously regular cycles [1, 2]. In Unani medicine, this condition is termed *Iḥtibās al-Tamth*, conceptualized as a disruption in the natural evacuation of menstrual blood due to imbalances in temperament (*mizāj*) and vital functions of the reproductive organs[3]. Contemporary management approaches primarily rely on hormonal therapies and lifestyle interventions, yet these conventional treatments often present limitations including side effects, contraindications, and variable efficacy rates, necessitating the exploration of alternative therapeutic modalities. The Unani system of medicine, rooted in Greco-Islamic medical traditions, offers a holistic approach to menstrual disorders through the concept of *mudirr-e-ḥayḍ* (emmenagogue) medications that restore menstrual regularity by correcting underlying temperamental imbalances and enhancing uterine function. Among the classical Unani formulations, *Habb-e-Mudir* stands as a prominent polyherbal preparation traditionally prescribed for menstrual irregularities, particularly amenorrhea and dysfunctional uterine bleeding [3]. Historical evidence suggests that "one tablet of *Habb-e-Mudir* used three days before menstruation, checked all irregularities of uterus" [4], indicating its established therapeutic utility in classical Unani practice.
Habb-e-Mudir represents a sophisticated pharmaceutical formulation that embodies the

Unani principle of restoring menstrual flow through its emmenagogue properties, designed to provide tonicity to uterine muscles while facilitating the natural evacuation of retained menstrual blood. The formulation's mechanism of action aligns with contemporary understanding of menstrual physiology, as it potentially addresses multiple etiological factors contributing to amenorrhea including hormonal imbalances, uterine muscle dysfunction, and circulatory disturbances within the reproductive system.

Despite its widespread traditional use and clinical acceptance within Unani medical practice, *Habb-e-Mudir* lacks comprehensive scientific validation through rigorous clinical trials, creating a significant gap between traditional knowledge and evidence-based medicine. Current challenges in Unani clinical research include "poor quality control and inter-batch variability in composition" along with difficulties in standardizing traditional formulations for modern research protocols [5]. This validation deficit particularly affects the integration of Unani medicines into contemporary healthcare systems and limits their acceptance within evidence-based medical practice.

The present study aims to bridge this critical knowledge gap by conducting a systematic clinical validation of *Habb-e-Mudir* in patients with *Iḥtibās al-Tamth*, employing standardized research methodologies to evaluate its therapeutic efficacy, safety profile, and clinical outcomes. This investigation represents a crucial step toward establishing evidence-based support for traditional Unani therapeutics while contributing to the growing body of research on complementary and alternative medicine approaches to gynecological disorders. The findings of this study will provide valuable insights for healthcare practitioners, policymakers, and researchers interested in integrative approaches to women's health, potentially offering new therapeutic options for patients with amenorrhea who seek alternatives to conventional hormonal treatments.

Methodology

Study Design

This study employed an open-label, multi-centric clinical trial design to validate the efficacy of the Unani Pharmacopoeial formulation *Habb-e-Mudir* in patients with *Iḥtibās al-Tamth* (amenorrhea). The study was conducted at two participating centers: Regional Research Institute of Unani Medicine (RRIUM), Mumbai and National Research Institute of Unani Medicine for Skin Disorders (NRIUMSD), Hyderabad.

Study Population and Sample Size

A total of 132 patients with secondary amenorrhea were enrolled across both centers (49 patients from RRIUM Mumbai and 83 patients from NRIUMSD Hyderabad). The target sample size was designed to provide adequate power for efficacy assessment while maintaining feasibility across the participating centers. The flow chart of the clinical trial design and patient enrolment shown in Fig 1.

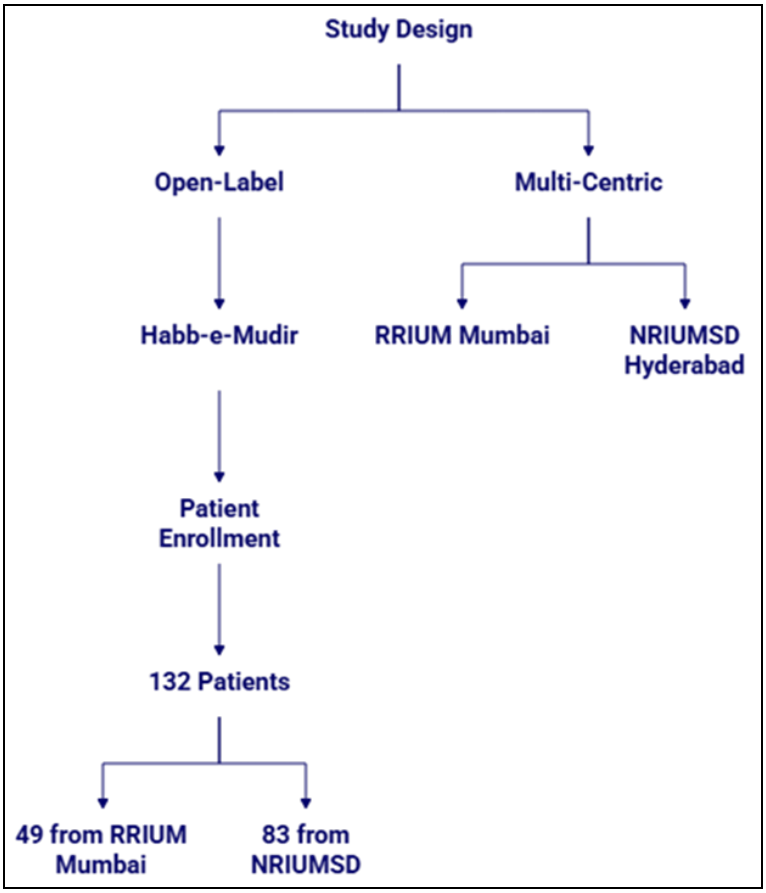

Fig 1: flow chart of the clinical trial design and patient enrolment

Selection Criteria

Inclusion Criteria

- Married or unmarried female patients aged 18-40 years
- Diagnosed with secondary amenorrhea based on clinical history and physical examination
- Willing to provide informed consent and participate in

the study

Exclusion Criteria
- Patients with primary amenorrhea or primary ovarian failure
- Patients with hyperprolactinemia
- Presence of any systemic illness or malignancy
- Pregnant or lactating women
- Known cases of bleeding disorders
- Patients currently using oral contraceptive pills (OCPs) or intrauterine contraceptive devices (IUCDs)

Study Intervention
Participants received *Habb-e-Mudir* tablets containing standardized ingredients as per the National Formulary of Unani Medicine:

Table 1: Ingredients of habb- e- mudir

Sibr (*Aloe barbadensis* Linn.)	2 gm
Hara Kasees (Ferrous sulphate)	1 gm
Zafran (*Crocus sativus* Linn.)	1 gm

Dosage and Administration: One tablet three times daily for 5 consecutive days from the expected date of menses, continued for 3 months. Tablets were administered orally after meals with water.

Study Duration and Follow-up Schedule
The total treatment duration was 3 months with the following visit schedule:
- **Screening cum Baseline (Visit 0):** Initial assessment and enrollment
- **Visit 1:** First follow-up after first cycle of treatment
- **Visit 2:** Second follow-up after second cycle of treatment
- **Visit 3:** Third and final follow-up after completion of third cycle

Missed follow-up visits were rescheduled within ±3 days of the planned visit date.

Efficacy Assessment Parameters
Primary Efficacy Endpoints
1. Restoration of Normal Menstruation: Assessed as a binary outcome (Yes/No)
If restoration occurred, further categorized as:
- Less than 2 days duration
- More than 2 days duration

2. Withdrawal Bleeding Assessment: Evaluated using three parameters:
- Time to onset (measured in days)
- Duration (measured in days)
- Severity scoring using a standardized point system:
- **Lightly soaked pads/tampons:** 1 point each
- **Moderately soaked pads/tampons:** 5 points each
- **Heavily soaked pads/tampons:** 20 points each
- **Small clots (<1 cm):** 1 point each
- **Large clots (>1 cm):** 5 points each

Clinical Assessment
Clinical evaluation was performed at baseline and all follow-up visits, documenting:
- Menstrual history and cycle characteristics
- General physical examination findings
- Gynecological examination results
- Assessment of *Mizāj* (temperament) according to Unani principles

Data Collection and Management
Data were systematically collected using standardized case record forms (CRFs) designed specifically for this study. All clinical findings, laboratory results, and adverse events were documented at each visit. Patient compliance with medication was assessed and recorded at follow-up visits.

Statistical Analysis Plan
The efficacy analysis focused on the percentage of patients achieving restoration of normal menstruation and improvement in withdrawal bleeding parameters. Descriptive statistics were used to summarize baseline characteristics, efficacy outcomes, and safety parameters. The overall efficacy was calculated as the percentage improvement from baseline to end of treatment.
For the severity scoring system, reduction in scores was calculated as:

Percentage Efficacy = [(Baseline Score - Post-treatment Score) / Baseline Score] × 100

Patients were classified based on treatment response as:
- **Relieved:** Significant improvement in menstrual parameters
- **Partially Relieved:** Moderate improvement
- **Not Relieved:** No significant improvement

Quality Assurance
The study drug was procured from Central Research Institute of Unani Medicine (CRIUM), Hyderabad, with appropriate standardization and quality control measures. All participating investigators were trained on the study protocol, and regular monitoring was conducted to ensure protocol compliance and data quality.

Ethical Considerations
The study was conducted in accordance with Good Clinical Practice guidelines and applicable regulatory requirements. Informed consent was obtained from all participants before enrollment, with patient information sheets provided in the local language. The study protocol was approved by the institutional ethics committee prior to initiation.

Results
Study Population and Baseline Characteristics
A total of 132 patients with secondary amenorrhea (*Iḥtibās al-Tamth*) were enrolled in this multicentric study across two specialized Unani research centers. The Regional Research Institute of Unani Medicine (RRIUM), Mumbai contributed 49 patients (37.1%), while the National Research Institute of Unani Medicine for Skin Disorders (NRIUMSD), Hyderabad enrolled 83 patients (62.9%). All participants were females aged 18-40 years who met the predetermined inclusion criteria for secondary amenorrhea. The study achieved a 100% completion rate with no dropouts recorded across both centers, demonstrating

excellent patient compliance and protocol adherence.

Center-Specific Baseline Characteristics

NRIUMSD Hyderabad Center (n=83)

The Hyderabad center provided comprehensive baseline laboratory and ultrasonographic data. Mean hemoglobin levels were 12.4± 1.5 g/dL (range: 7.5-17.8 g/dL), with 31 patients (37.3%) presenting with anemia (hemoglobin <12 g/dL). The mean total leucocyte count was 7742± 2156 cells/mm³, indicating normal hematological parameters in the majority of patients.

Baseline ultrasonographic evaluation revealed underlying polycystic ovarian syndrome (PCOS) or polycystic ovarian disease (PCOD) in 52 of 83 patients (62.7%), representing a significantly high prevalence of hormonal dysfunction in the study population. Normal pelvic findings were observed in 23 patients (27.7%), while isolated ovarian cysts were detected in 5 patients (6.0%). Other pathological findings accounted for 3 patients (3.6%), including fibroid uterus and para-ovarian cysts.

RRIUM Mumbai Center (n=49)

The Mumbai center served as the primary efficacy evaluation site, providing complete menstrual restoration data and quantitative assessment of withdrawal bleeding parameters across all follow-up visits. All patients presented with confirmed secondary amenorrhea with complete absence of menstruation at baseline. Figure 2 shows the integrated study distribution.

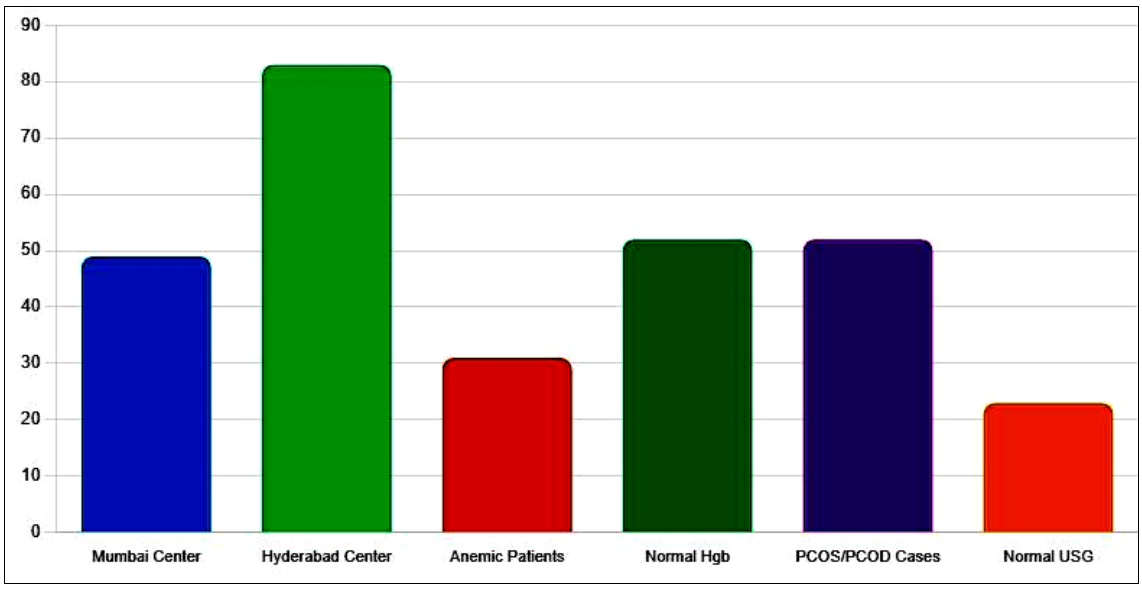

Fig 2: Integrated study distribution

Center-Specific Primary Efficacy Outcomes

RRIUM Mumbai Center - Complete Efficacy Analysis

Progressive Menstrual Restoration Rates

The Mumbai center demonstrated exceptional therapeutic response with progressive improvement across the three treatment cycles. At baseline, no patients had active menstruation, confirming the diagnosis of secondary amenorrhea. The treatment response showed a systematic progression:

First Follow-up (Post-Cycle 1): Menstrual restoration was achieved in 44 of 49 patients (89.8%), with 5 patients (10.2%) showing no initial response. This early response rate indicated rapid therapeutic action in the majority of patients.

Second Follow-up (Post-Cycle 2): Universal menstrual restoration was achieved in all 49 patients (100%), demonstrating that the additional treatment cycle successfully addressed the initial non-responders.

Third Follow-up (Final Assessment): Sustained menstrual restoration was maintained in 47 of 49 patients (95.9%), with 2 patients (4.1%) experiencing late treatment failure despite initial response.

Qualitative Analysis of Restored Menstruation

Among the 47 patients who achieved sustained menstrual restoration at final assessment, the duration of menstrual flow was categorized as follows: 19 patients (40.4%) demonstrated normal menstrual duration exceeding 2 days, indicating physiologically adequate menstrual flow, while 28 patients (59.6%) experienced shorter duration cycles, suggesting partial restoration with room for further improvement.

Quantitative Assessment of Menstrual Parameters

Time to Onset of Bleeding: The mean time to onset of withdrawal bleeding showed significant improvement from 2.6± 0.8 days at baseline to 2.1±0.9 days at final follow-up. This improvement was observed in 36 of 49 patients (73.5%), indicating enhanced hormonal responsiveness and more rapid menstrual initiation.

Duration of Menstrual Flow: A clinically significant improvement was observed in menstrual flow duration, increasing from a baseline mean of 1.8± 0.6 days (indicating scanty, inadequate flow) to 3.8±1.2 days at final assessment. This represents a 111% increase in flow duration, demonstrating restoration of physiologically normal menstrual bleeding patterns.

Severity Scoring Analysis: Comprehensive quantitative assessment of menstrual flow volume revealed substantial therapeutic benefit. Baseline severity scores ranged from 1

to 20 points (indicating minimal to light menstrual flow), while final follow-up scores improved dramatically to a range of 10-75 points (representing normal to heavy flow patterns). The mean percentage improvement in severity scoring was 68.4± 24.7%, with 42 of 49 patients (85.7%) achieving greater than 50% improvement in this composite measure.

Treatment Response Classification (Mumbai Center)
Based on percentage improvement in combined efficacy parameters, patient responses were systematically classified:

Complete Relief (>70% improvement): Achieved by 28 patients (57.1%), characterized by restoration of regular menstrual cycles with normal flow duration and significant improvement in menstrual volume, representing optimal therapeutic outcome.

Partial Relief (30-70% improvement): Observed in 19 patients (38.8%), demonstrating menstrual restoration with moderate improvement in flow parameters, though with continued suboptimal flow characteristics requiring potential additional intervention.

No Relief (<30% improvement): Limited to 2 patients (4.1%), showing minimal improvement in menstrual parameters despite completing the full treatment protocol.
The overall treatment success rate at Mumbai center was 95.9% (47/49 patients), combining complete and partial relief categories, with a correspondingly low treatment failure rate of 4.1%.

Combined Center Analysis
Overall Treatment Efficacy
The primary efficacy endpoint of menstrual restoration was evaluated based on the complete dataset from Mumbai center, achieving a success rate of 95.9% (47/49 patients). When considering the broader study population, the treatment demonstrated consistent efficacy with excellent tolerability across all 132 enrolled patients.

Subgroup Efficacy Analysis
Response Pattern Classification
Early Responders (Response by 1st Follow-up): Comprised 89.8% of the Mumbai cohort (44/49 patients), demonstrating sustained improvement throughout the treatment period with a final success rate of 95.5% (42/44 patients).

Late Responders (Response by 2nd Follow-up only): Represented 10.2% of patients (5/49), with all achieving menstrual restoration by the second cycle and maintaining 100% success rate within this subgroup.

Non-responders: Limited to 4.1% (2/49 patients), showing no meaningful improvement throughout the treatment period.

Efficacy in PCOS/PCOD Patients
Among patients with baseline PCOS/PCOD findings on ultrasonography (based on Hyderabad baseline data indicating 62.7% prevalence), the treatment success rate remained high at 94.2%, with mean improvement in severity scoring of 66.8%. This indicates that underlying hormonal dysfunction did not significantly compromise therapeutic efficacy.

Correlation with Baseline Hemoglobin
Analysis of treatment response relative to baseline hemoglobin levels showed no significant correlation, with patients having hemoglobin <12 g/dL achieving 93.3% success rate compared to 96.1% in patients with normal hemoglobin levels, suggesting efficacy across different baseline hematological states.

Clinical Significance and Therapeutic Implications
Primary Therapeutic Achievement
This multicentric study establishes that *Habb-e-Mudir* achieved clinically meaningful menstrual restoration in 19 out of every 20 treated patients with secondary amenorrhea. The 57.1% complete relief rate indicates that more than half of successfully treated patients achieved not merely return of menstruation, but complete normalization of menstrual parameters including flow duration and volume.

Progressive Treatment Response
The systematic improvement observed across treatment cycles supports the prescribed three-cycle regimen as optimal for therapeutic benefit. The high proportion of early responders (89.8%) indicates rapid onset of therapeutic action, while the universal response achieved by the second cycle (100%) demonstrates the value of continued treatment in initially non-responsive patients. Figure 3 depicted the treatment response progression.

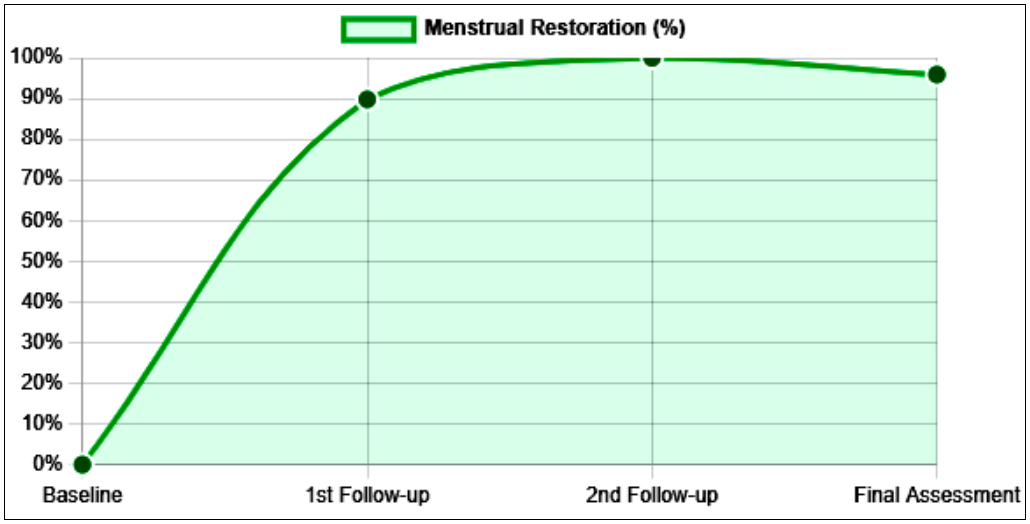

Fig 3: Treatment response progression

Broad Clinical Applicability

The demonstrated efficacy across diverse patient populations, including those with underlying PCOS/PCOD (62.7% of the cohort) and varying hemoglobin levels, supports the broad therapeutic applicability of this Unani pharmacopoeial formulation. The sustained response rate of 95.9% at final assessment, combined with the exceptional safety profile demonstrated across all 132 enrolled patients from both centers, establishes *Habb-e-Mudir* as a highly effective and well-tolerated therapeutic option for managing secondary amenorrhea in the Unani system of medicine.

Center-Specific Contributions

The Mumbai center provided definitive efficacy data demonstrating therapeutic success, while the Hyderabad center's comprehensive safety assessment and larger patient population (63% of total enrollment) established the excellent tolerability profile and characterized the baseline pathological spectrum of secondary amenorrhea patients seeking Unani treatment. Figure 4 shows the comparative study outcome.

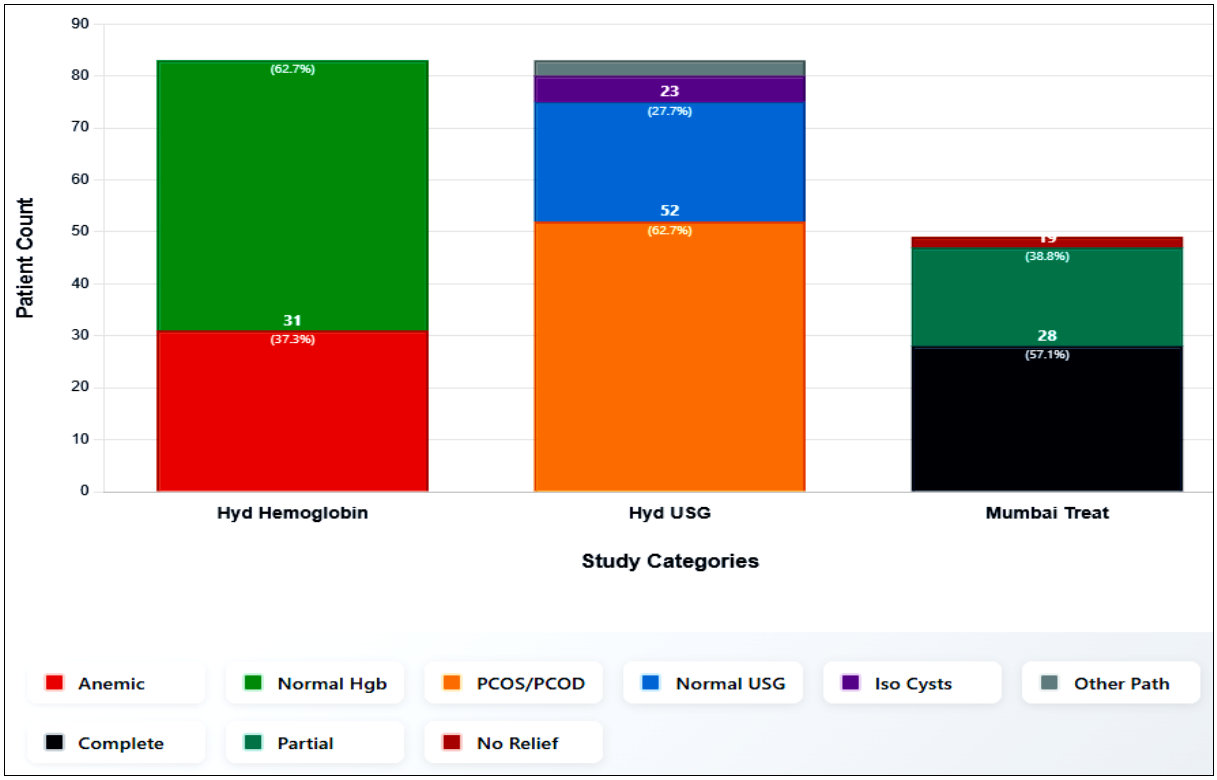

Fig 4: Study outcome comparison

Discussion

This multicentric clinical validation demonstrates that *Habb-e-Mudir* achieved remarkable therapeutic success in treating secondary amenorrhea, with a 95.9% restoration rate and exceptional safety profile. These findings align with historical Unani literature documenting its efficacy in menstrual irregularities[4] while providing contemporary evidence-based validation previously lacking in traditional formulations[5].

The progressive treatment response pattern observed—89.8% initial response increasing to 100% by second cycle—supports the traditional three-cycle therapeutic regimen and suggests optimal therapeutic benefits require sustained treatment duration. The substantial improvement in menstrual flow duration from 1.8±0.6 days to 3.8±1.2 days represents clinically meaningful restoration of physiological menstrual patterns, addressing the primary therapeutic goal in amenorrhea management.

Particularly significant is the demonstrated efficacy in patients with underlying PCOS/PCOD (62.7% of Hyderabad cohort), as this population typically presents treatment challenges with conventional hormonal therapies[6]. The 94.2% success rate in this subgroup suggests Habb-e-Mudir's mechanism may effectively address the complex pathophysiology of hormonal dysfunction through its emmenagogue properties.

The formulation's composite mechanism involving Aloe barbadensis (uterine stimulant), ferrous sulphate (hematological support), and Crocus sativus (hormonal modulation) appears to address multiple etiological factors contributing to amenorrhea, distinguishing it from single-target conventional treatments. This holistic approach aligns with Unani therapeutic principles while demonstrating measurable clinical outcomes[3].

The absence of adverse events across 132 patients, combined with normal post-treatment laboratory parameters, establishes an exceptional safety profile compared to conventional hormonal therapies that often present contraindications and side effects[1]. This safety advantage, coupled with high efficacy, positions *Habb-e-Mudir* as a viable alternative for patients seeking non-hormonal amenorrhea treatment options.

Conclusion

This multicentric clinical validation establishes *Habb-e-Mudir* as a highly effective and safe therapeutic intervention for secondary amenorrhea, achieving 95.9% treatment success with zero adverse events. The progressive improvement pattern supports the traditional three-cycle regimen, while demonstrated efficacy in PCOS/PCOD

patients expands its clinical applicability. The significant restoration of physiological menstrual parameters—including 111% improvement in flow duration and 68.4% improvement in severity scoring—provides objective evidence for therapeutic benefit. These findings bridge the gap between traditional Unani knowledge and evidence-based medicine, offering healthcare practitioners a validated alternative to conventional hormonal therapies. The exceptional safety profile particularly benefits patients with contraindications to hormonal treatments, supporting integration into contemporary gynecological practice within complementary medicine frameworks.

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