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Original Article

A Randomized Comparative Study of Unani Formulations in Abnormal Uterine Bleeding due to Endometrial Hyperplasia

Abothu Suhasini[1*], Wasia Naveed[2] , Arshiya sultana[3*] , Shahzadi Sultana[4]

[1]*Professor, Department of Ilmul Qabalat wa Amraze Niswan (Gynaecology and Obstetrics), Govt. Nizamia Tibbi College, Hyderabad, Telangana.*
[2] *Department of Ilmul Qabalat wa Amraze Niswan (Gynaecology and Obstetrics), Govt. Nizamia Tibbi College, Hyderabad, Telangana.*
[3]*Professor, Department of Ilmul Qabalat wa Amraze Niswan (Gynaecology and Obstetrics), National Institute of Unani Medicine, Ministry of AYUSH, GOI, Bengaluru 560091, Karnataka, India*
[4]*In-Charge Principal & HoD, Department of Ilmul Qabalat wa Amraze Niswan (Gynaecology and Obstetrics), Govt. Nizamia Tibbi College, Hyderabad, Telangana*

ABSTRACT

Objectives: To compare the efficacy of polyherbal Unani formulations in heavy menstrual bleeding due to endometrial hyperplasia.

Methodology: A prospective, randomized comparative trial was conducted at Govt. Nizamia Tibbi College. Group A (n=20) received *Itrifal Aftimoon* 5g orally BID from menstruation day 3 to day 21 plus suprapubic *Marham Dakhilyun* application and per vaginally *Marham Dakhilyun* (5g) and *Roghan Gul* (10ml) application from menstruation day 5 to day 14. Group B (n=20) received *Gulnar Farsi* (2g), *Phitakri Biryan* (0.25g), *Dammul Aqwain* (0.25g), and *Geru* (2g), 2.5g powder orally BID, menstruation day 3 for 20 days plus *Douche Bargh Sambhalu* then *Ḥamūl* of *Safuf Mazu* (*2g*), *Kalijiri* (2g) and *Roghan Gul* (10ml) from menstruation day 3 to day 12 for 3 consecutive cycles. The primary outcome was pelvic ultrasound findings of endometrial thickness. The secondary outcome measures were improvement in haemoglobin percentage, change in menstrual flow and menstrual pattern. The level of significance was 5%.

Results and conclusion: The intragroup comparison showed that the mean endometrial thickness at baseline and after treatment in groups A and B was extremely significantly different (P<0.0001). The intragroup comparison showed the mean haemoglobin percent at baseline and after treatment in group, A was significantly different (P<0.0001). After treatment, 50% and 60% of participants had normal duration and menstrual blood loss after treatment from baseline in Groups A and B respectively. However, further, phase II and III randomized standard controlled trials in larger samples are recommended to assess the efficacy of these group medicines.

Keywords: Astringent; Endometrial hyperplasia; Endometrial tissue; Humours; Unani Medicine

INTRODUCTION

Endometrial hyperplasia (EH) is a non-physiological, pre-cancerous, non-invasive proliferation of the endometrium that causes changes in the size and structure of the glandular tissue as well as an increase in the volume of endometrial tissue. Additionally, an endometrial gland-to-stroma ratio greater than 1:1 is the outcome. The prevalence of EH is currently estimated to be around 200,000 new cases per year in Western countries.[1] The condition is most common in women over 40, with the peak incidence occurring between the ages of 40 and 45. The most typical sign of EH is abnormal uterine bleeding (AUB), which includes irregular bleeding, intermenstrual bleeding, menorrhagia, and postmenopausal haemorrhage. [1]Abnormal uterine bleeding (AUB) refers to any form of bleeding that does not fall within the usual parameters for frequency, amount, duration, or cyclicity. 20% of

*Correspondence: Abothu Suhasini, Arshiya sultana
E-mail: drasuhasini@yahoo.com; drarshiya@yahoo.com
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outpatient visits and nearly 25% of gynaecological surgeries are accounted for by AUB. AUB accounts for almost 25% of gynaecological operations and 20% of outpatient visits. [2,3] According to another study, the majority of females with EH will have AUB when they show clinically. EH was once thought to be responsible for 15% of all cases of post-menopausal haemorrhage.[4]

The risk factor for early menarche, chronic anovulation, infertility, age >35 years, diabetes milletus, PCOS, smoking, obesity, nulliparity, late onset of menopause[4] and several other conditions associated with increased oestrogen levels/steroid hormone imbalances are risk factors for EH. Anovulation and polycystic ovarian syndrome (PCOS) cause unchecked estrogenic activity in the endometrium. [1]

The majority of instances of EH are caused by persistent oestrogen exposure that is unopposed by progesterone (as in previous versions of hormone replacement treatment (HRT)). Furthermore, in obese women, oestrogen overproduction by fat cells adds to an increased risk of EH and endometrial cancer (EC). Oestrogen not only induces proliferation but also induces morphometric alterations in the uterus i.e., the gland-to-stroma ratio, changes in the type of luminal and glandular epithelia, the number and shape of glands and the morphology of epithelial cells. [1, 4] Endometrial disorders induce abnormal uterine bleeding due to local abnormalities in endometrial function such as inflammation and hypoxia, which have a deleterious influence on normal angiogenesis, vascular integrity, hemostasis, or endometrial healing. Furthermore, PGF2 and Endothelin-1 are local vasoconstrictors that promote uterine spiral arteriole vasoconstriction and limit blood loss during menstruation. The presence of AUB is triggered by a lack of these vasoconstrictors. Furthermore, increased synthesis of vasodilators such as PGE2 and PGI2 has been seen in patients with AUB. HMB is also associated with less maturation of the spiral arteriole vessel wall, less vascular smooth muscle, and more gaps in the endothelial cell lining.[5]

Currently, treatment options for EH, including hormone therapy or hysterectomy, are insufficient. Progestins are frequently employed to treat EH without atypia. Despite the reality that hormonal care of women with EH is mainly based on case studies, the effectiveness of which has not been extensively evaluated. The scarcity of mainstream and conservative treatment options underlines the need for novel and alternative medicines. [1]

The Unani classic texts do not give a specific name for endometrial hyperplasia. However, endometrial hyperplasia possibly may be described under *Waram al-Rahim. Waram al-Rahim* is of three types usually *Ḥārr* and *Sulb* are common and sometimes *Balghamī* is also noted. *Waram* affects the fundus of the uterus or all 4 sides or the whole uterus. One of the causes would be the *Insibab* of *Damawī* or *Ṣafrāwī Māddī* the coldness that inhibits the flow of *Māddī* and causes *Waram Sulb Sawdāwī*.[6] *Waram al-Rahim Ḥārr* which further comprises *Waram al-Rahim Damawī* and *Ṣafrāwī* and *Waram al-Rahim Bārid* which includes *Waram al-Rahim Balghamī* and *Sawdāwī*. [7] The temperament of female genital organs i.e., uterus, ovaries and the associated arteries is also hot and moist. Hence, there are definite changes in temperament from hot and moist to cold and dry with the advancement of age. The condition of EH is swelling of the inner muscular layer of the uterus which is caused by humoral abnormality leading to temperament disturbance. Unani medicine that is helpful in *Amrad Bārida, Waram-i-Sawdāwī* such as *Itrifal Aftimoon, Marham Dakhilyun* Ointment,[8] *Phitakri Biryan, Dammul Aqwain, Geru*, *Bargh Sambhalu, Mazu, Kalijiri*, and *Roghan Gul* [9] are useful to treat endometrial hyperplasia and abnormal uterine bleeding that possess *Muhallil Waram, Habis, Qabiz, Mundij Sawdā',* etc properties. [9] Although these plant and mineral products are mentioned in classical texts and are frequently used, however, not validated.

Hence, this study was to compare the efficacy of two Unani regimens in abnormal uterine bleeding associated with endometrial hyperplasia using the aforementioned Unani medicine.

Materials and methods

Study design, setting, protocol approval and consent: A simple randomized parallel open-labelled comparative study was conducted at Govt Nizamia Tibbi College, Telangana India from November 2005 to May 2006. The protocol was approved (Reg No.10/250/03 DRNTRUHS dt: 26/12/2006) by Dr NTR University of Health Sciences and all the patients gave written consent before initiation of the study.

Participants: The participants were recruited based on the signs and symptoms of abnormal uterine bleeding and endometrial thickness in pelvic ultrasonography and endometrial biopsy reports.

Inclusion and exclusion criteria: Female married patients of premenopausal age with changes in the menstrual pattern, and abnormal uterine bleeding with thickened endometrium>8mm in transabdominal or transvaginal pelvic ultrasonography were included in the study.[10] Participants who underwent diagnostic dilation and curettage (DD&C) for diagnosis of the type of endometrial hyperplasia were included. The exclusion criteria were patients who showed cytological atypia on DD&C, blood dyscrasias, and other medical disorders.

Procedure: All the participants underwent assessment including history, physical examination, and blood investigations such as haemogram, random blood sugar, HIV, HbsAg, VDRL, Serum T3, T4, TSH, bleeding time, clotting time and platelet count before treatment. Transabdominal or transvaginal pelvic ultrasonography was carried out for endometrial thickness before treatment. Before treatment, all participants underwent diagnostic dilation and curettage (DD&C) for diagnosis of the type of endometrial hyperplasia. Post-treatment transabdominal or transvaginal pelvic ultrasonography was repeated in all participants for endometrial thickness. DD&C was carried out in participants who were willing for the procedure or who had an endometrial thickness of more than 11 mm after treatment. Follow-up visits were scheduled for 20 days for 3 consecutive cycles commencing from the 3rd day of the menstrual cycle.

Data collection tool: For data collection endometrial thickness was measured by transabdominal or transvaginal pelvic ultrasonography before and after treatment. The cut-off value for endometrial thickness (ET) was 8-10 mm. Previous studies showed that the cut-off ET value was 8 mm with sensitivity and specificity of 83.9%, and 58.8%, respectively, and 90.4% negative predictive value for abnormal endometrium. [10] Haemoglobin percentage was measured by Sahli's method before and after treatment. The duration of menstrual flow was observed in the days before and after treatment. The normal cut-off for the duration of menstrual flow was taken as 6 days.

Intervention

Group A: Medicine included in group A were *Itrifal Aftimoon, Marham Dakhilyun* and *Roghan Gul* (Table 1).

Preparation and dosage: *Itrifal Aftimoon* was prepared by the Institute pharmacy. All the ingredients were dried and powdered in the grinder. Then the powder was sieved. *Itrifal* was prepared as mentioned in the traditional Pharmacopoeia. *Marham Dakhilyun* was directly purchased from the local market by the Hamdard company. Group A (n=20) received *Itrifal Aftimoon,* 5g orally twice daily after meals from day 3 of menses for 20 days plus suprapubic liniment application of *Marham Dakhilyun* and per vaginally *Ḥamūl* of *Marham Dakhilyun* (5g) and *Roghan Gul* (10ml) advised for 10 days from day 5 of menses. Table 1 Summarizes the ingredients of *Itrifal Aftimoon* and *Marham Dakhilyun.*

Group B: Medicine included in group B were powder of *Gulnar Farsi*, *Phitakri Biryan*, *Dammul Aqwain*, *Geru, Bargh Sambhalu, Safuf Mazu*, *Kalijiri* and *Roghan Gul.*

Preparation and dosage: Group B (n=20) received 2.5g powder of *Gulnar Farsi* (2g), *Phitakri Biryan* (0.25g), *Dammul Aqwain* (0.25g), and *Geru* (2g), orally twice daily after meals from day 3 of menses for 20 days plus *Douche* of *Bargh Sambhalu* followed by *Ḥamūl* of *Safuf Mazu* (2g), *Kalijiri* (2g) and *Roghan Gul* (10ml) for 10 days from day 5 of menses for 3 consecutive cycles.

Assessment of efficacy: The primary outcome included a change in pelvic ultrasound findings of endometrial thickness. The secondary outcome included improvement in haemoglobin and decrease in the duration of menstrual flow and a change in menstrual pattern.

Randomization and allocation: A total of 40 patients with AUB were recruited at random and assigned to either Group A or Group B in a 1:1 ratio using a lottery strategy. We used an open list of random numbers.

Sample size estimation: The sample size was calculated using sample size calculator software and was based on an earlier study's proportion value of cure rate of 20% and 39%.[11] The study would require a total sample size of 44 (n1=22 and n2=22), 5% significance, and 80% power. As a result, in the current study, a sample size of 40 patients was chosen, with a 20% dropout rate allowed.

Data analysis: The data was analyzed utilizing the statistical software Graph Pad Instat version 3.00 for Windows (Graph Pad Software, San Diego, Calif, USA). P0.05 was deemed significant for all statistical tests. All deviations from the baseline were compared between groups.

Table 1. Ingredient of *Itrifal Aftimoon* and *Marham Dakhilyun* Ointment[8]

S. No.	Unani Name	Botanical name	Quantity (g)
Itrifal Aftimoon			
1.	*Post Halela Kabuli*	*Terminalia chebula* L.	45
2.	*Amla*	*Embelica officinalis* L.	45
3.	*Post Balela*	*Terminalia bellerica* L.	45
4.	*Turbud Sufed*	*Operculina turpethum* L.	22.5
5.	*Aftimoom vilayati*	*Cuscuta reflexa* Roxb.	22.5
6.	*Sana Makki*	*Cassia angustfolia* Vahl	22.5
7.	*Sheetraj Hindi*	*Plumbago zeylanica* L.	22.5
8.	*Bisfayej Fasthaqi*	*Polypodium vulgare* L.	22.5
9.	*Ustukhuddus*	*Lavandula stoechas* L.	22.5
10.	*Gul Surkh*	*Rosa damescene*	22.5
11.	*Anisoon*	*Pimpinella anisum* L.	9
12.	*Namak Hindi*		9
***Marham-e-Dakhilyun* Ointment**			
S. No.			
1.	*Raughan Zaitoon*	*Oleo europaea* L. oil	120
2.	*Murdarsang*	Plumbi oxidum	60
3.	*Tukhm Khatmi*	*Althea officinalis* L. seeds	20
4.	*Mako*	*Solanum nigrum* F. fruit	20
5.	*Tukhm Katan*	*Linum usitatissimum* L seeds	20
6.	*Aspaghol*	*Plantago ovata* L. seeds	20
7.	*Tukhme Hulba*	*Trigonella foenum-graecum* L.	20

8.	*Mom Zard*	Bee Wax	Quantity required

Results

Participants flow: During the study period, a total of 73 patients were screened for abnormal uterine bleeding. Thirty-three patients were omitted from the trial for various reasons. Then, 40 patients were assigned to groups A and B at random **(Figure 1).**

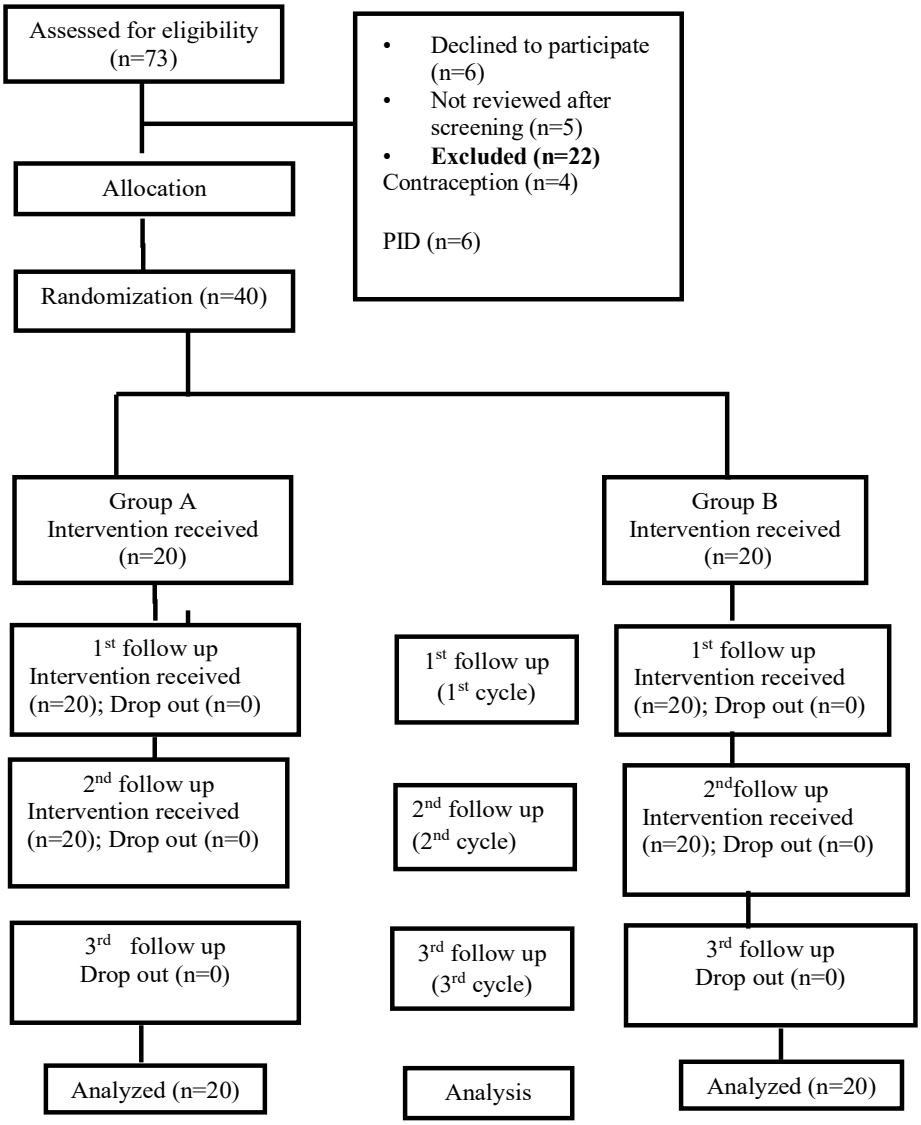

Fig 1: Flow Chart of participants as per Consort statement

Socio-economic, gynaecological and obstetrics parameters at baseline in groups A and B: The variables were comparable between groups (age, socio-economic status, religion, occupation, contraceptive history, per vaginal examination, parity, and last childbirth) at baseline. The mean age in group A was 40±5.1 and B was 41±6 years. Maximum participants were between 36-45 years of age [group A: n=10/20 (50%) and group B: n=7/20 (35%)]. Maximum participants were from middle socio-economic status [group A: n=12/20 (60%) and group A: n=10/20 (50%)]. There was no statistical difference in mean baseline measurements between the groups (Table 2).

Table 2. Sociodemographic, gynaecological and obstetrics parameters in both groups

Variables	**Group A (n=20) No of patients**	**Percentage**	**Group B (n=20) No of patients**	**Percentage**	**Total (n=40) No of patients**	**Percentage**	***P* value**
Age (yrs)							
30-35	3	15	6	30	9	22.5	0.05[a]
36-40	10	50	3	15	13	32.5	
41-45	2	10	7	35	9	22.5	
46-50	4	20	4	20	8	20	
Religion							
Christian	0	0	0	0	0	0	1.00[a]
Hindu	0	0	1	5	1	2.5	
Muslim	20	100	19	95	39	97.5	
Occupation							
Housewife	20	100	20	100	40	100	
Socio-economic status							
Lower	5	25	4	20	9	22.5	0.523[a]
Middle	12	60	10	50	22	55	
Upper	3	15	6	30	9	22.5	
Per vaginal examination							
Uterus Anteverted	16	80	16	80	32	80	1.00[b]
Retroverted	4	20	4	20	8	20	
Parity							
≤2	3	15	4	20	7	17.5	0.8[a]
3-4	10	50	8	40	18	45	
≥5	7	35	8	40	15	37.5	
Last childbirth							
≤2	3	15	1	5	4	10	0.3[a]
3-4	1	5	3	15	4	10	
≥5	16	80	17	85	32	80	

Contraceptive history							
Tubectomised	14	70	13	65	27	67.5	0.73 [b]
Not tubectomised	6	30	7	35	13	32.5	

Test used: [b]Chi-square; [a]Fisher Exact Test

Duration of illness, menstrual bleeding pattern and associated symptoms in groups A and B at baseline: Maximum participants had a duration of illness between one to three months in both groups (Group A: n=8/20, 40%; Group B: n=8/20, 40%) at baseline. Maximum participants had heavy menstrual bleeding with prolonged duration of menstrual flow in both groups (Group A: n=12/20, 60%; Group B: n=11/20, 55%) at baseline. Other details are summarized in Table 3.

Table 3. Duration of illness, menstrual pattern and associated symptoms in groups A and B

Variables	**Group A (n=20) No of patients**	**%**	**Group B (n=20) No of patients**	**%**
Duration of illness (Months)				
1-3	8	40	8	40
3-6	5	25	7	35
6-9	1	5	2	10
9-12	4	20	2	10
>12	2	10	1	5
Menstrual bleeding pattern				
Heavy menstrual bleeding	12	60	11	55
Indefinite continuous bleeding	2	10	5	25
Amenorrhoea followed by bleeding	2	10	1	5
Intermenstrual bleeding	1	5	1	5
Irregular bleeding	3	15	2	10
Associated symptoms				
Pain abdomen	19	95	18	90
Backpain	12	60	12	60
Abnormal vaginal discharge	16	80	18	90

Number and Percentage

Investigations in both groups at baseline: The haematological, biochemical, histopathological and pelvic Ultrasonography variables were comparable between groups before treatment (Hb%, T3, T4, and TSH). HIV, HBsAg, and VDRL were normal in all patients. Maximum participants had simple endometrial hyperplasia in both groups (Group A: n=14/20, 70%; Group B: n=13/20, 65%) and thickened endometrium in pelvic ultrasonography (Group A: n=13/20, 65%; Group B: n=15/20, 75%) (Table 4).

Table 4. Investigations in both groups

Investigations	Group A (n=20)	Group B (n=20)	*P* value
HB% (gm/dl) Mean (SD)	10.75 (1.29)	10.08(1.19)	0.09[a]
T3 **(µIU/ml)** Mean (SD)	1.16(0.47)	1.25(0.41)	0.68 [a]
T4 **(µIU/ml)** Mean (SD)	9.18(3.4)	9.48(2.29)	0.74 [a]
TSH **(µIU/ml)** Mean (SD)	3.51(2.28)	3.86(2.11)	0.38 [a]
Histopathological finding in endometrial biopsy No (%)			
Simple hyperplasia	14 (70)	13(65)	0.98[b]
Adenomatous hyperplasia	2 (10)	2 (10)	
Cystic glandular hyperplasia	4 (20)	5 (25)	
Pelvic Ultrasonography findings			
Thickened endometrium	13(65)	15 (75)	0.78[b]
Thickened endometrium with PCOS	4(20)	3(15)	
Thickened endometrium with cystic ovary	3(15)	2(10)	

Number (%) and Mean (SD); [a] Independent t test; [b] Fisher Exact test

Primary and secondary outcomes in groups A and B at baseline and after treatment

Primary outcome: The primary outcome was a change in endometrial thickness in pelvic ultrasonography

Endometrial thickness in pelvic Ultrasonography: The mean endometrial thickness at baseline and after treatment in group A was 14.95 (3.00) and 7.75(3.12) mm respectively with a significant difference in *P* value <0.001. The mean endometrial thickness at baseline and after treatment in group B was 13.8(1.79) and 6.85 (2.58) mm respectively with a significant difference in *P* value <0.001. Group A and B comparisons at baseline (*P*=0.14) and after treatment (*P*=0.15) showed no statistical difference (see Table 5).

Secondary outcome: Secondary outcomes included improvement in haemoglobin and decrease in the duration of menstrual flow and a change in menstrual pattern.

Haemoglobin percentage: The mean haemoglobin per cent at baseline and after treatment in group A was 10.75 (1.29) and 11.62(0.99) per cent respectively with a significant difference in *P* value <0.0001. The mean haemoglobin per cent at baseline and after treatment in group B was 10.08(1.19) and 11.25(1.25) per cent respectively with significant differences in *P* value <0.0001. At baseline, between the group comparisons A and B showed not quite a statistical difference (*P*=0.09). After treatment, group A and B comparisons showed no statistical difference (*P*=0.68) (see Table 5).

Table 5. Primary and Secondary outcome

Outcomes	Group A (n=20) **No of patients**	Group B (n=20) **No of patients**	*P* value
Primary outcome			
Endometrium thickness in pelvis Ultrasonography [mean (SD)]			
Before treatment	14.95(3.00)	13.8(1.79)	0.14
After treatment	7.75(3.12)	6.85 (2.58)	0.15
P value	0.001	0.001	
Secondary Outcome			
Haemoglobin [mean (SD)]			
Before treatment	10.75 (1.29)	10.08(1.19)	0.09
After treatment	11.62(0.99)	11.25(1.25)	0.68
P value	0.001	0.001	

Student's t-test; Wilcoxon matched pair test and Mann-Whitney U test
P value< 0.001, considered extremely significant

Duration of menstrual flow and menstrual cycle in groups A and B at baseline and after treatment: Maximum participants had a duration of menstrual flow between 9 to 12 days in both groups (Group A: n=7/20, 35%; Group B: n=9/20, 45%) at baseline. After treatment duration of menstrual flow was less than 6 days in 50% (n=10) and 60% (n=12) participants respectively showing 50% and 60% of participants had normal duration and menstrual blood loss after normal menstrual bleeding was seen in 85% (n=17) and 90% (n=18) participants respectively showing 35% and 30% change after treatment from baseline in groups A and B respectively (see Table 6). treatment from baseline in groups A and B respectively. Maximum participants had a duration of the cycle between 25 to 35 days in both groups (Group A: n=9/20, 45%; Group B: n=12/20, 60%) at baseline. After treatment duration of the cycle between 25 to 35 days normal menstrual bleeding was seen in 85% (n=17) and 90% (n=18) participants respectively showing 35% and 30% change after treatment from baseline in groups A and B respectively (see Table 6).

Table 6. Duration of menstrual flow and menstrual cycle in groups A and B at baseline and after treatment

Menstruation	**Before treatment**				**After treatment**			
Duration of flow (Days)	**Group A (n=20) No of patients**	**%**	**Group B (n=20) No of patients**	**%**	**Group A (n=20) No of patients**	**%**	**Group B (n=20) No of patients**	**%**
< 6	0	0	0	0	10	50	12	60
6-9	5	25	4	20	3	15	6	30
9-12	7	35	9	45	3	15	1	5
12-15	3	15	1	5	0	0	1	5

15-18	1	5	0	0	4	20	0	0
>18	4	20	6	30	0	0	0	0
Duration of the cycle (Days)								
20-25	2	10	1	5	1	5	1	5
25-30	7	35	8	40	14	70	14	70
30-35	2	10	4	20	3	15	4	20
35-40	0	0	0	0	1	5	1	5
40-45	0	0	0	0	0	0	1	5
>45	4	20	1	5	1	5	0	0

Discussion

Both groups were equally effective in reducing endometrial thickness regularizing menstruation and decreasing heavy menstrual bleeding. Unani scholars said that the initial stages of *Waram-i-Sulb* sometimes are the melancholic type and are the result of chronic *Balghamī Waram*. This type of swelling may progress into carcinoma. Unani medicine that is helpful in *Amrade Bārid, Waram-i- Sawdāwī* such as *Itrifal Aftimoon, Marham Dakhilyun* Ointment, [8] *Phitakri Biryan, Dammul Aqwain, Geru*, *Bargh Sambhalu, Mazu, Kalijiri*, and *Roghan Gul* [9] are useful to treat endometrial hyperplasia and abnormal uterine bleeding that possess *Muhallil Waram, Habis, Qabiz, Mundij Sawdā',* etc properties. [9] Most of the aforementioned medicines have *Bārid wa Yābis* temperament including *Geru*, *Mazu*, and *Phitakri Biryan* [12] which helps in haemostasis. Moreover, *Kathrat-i-Hayd* is triggered by *Ḍu'f Quwwat Māsika* (weak retentive power) and *Qā*wi *Quwwat Dāfi'a* (strong expulsive power) and it is supposed that *Bārid wa Yābis* drugs tone up the *Quwwat Ghādhiya* of *Rahim* (nutritive power of uterus) and ultimately rectify the abnormality of *Quwwat Māsika* and *Quwwat Dāfi'a*. [12, 13] Furthermore, these medicines are pharmacologically proven for anti-inflammatory, anti-estrogenic, anti-proliferative, styptic as they possess tannins, flavonoids isoflavonoids, saponins, alkaloids, and other bioactive components (see table 7). [14, 15, 16] The response of the trial drugs in both groups was due to the *Qabiz* (astringent) property which helps to control excessive bleeding and these herbs with astringent activity also produce a protective coating on the tissue surface.[17]

Although the particular mechanism of action of these herbs is unknown, it has been hypothesized that these plant components and minerals are useful because they have been demonstrated for astringent, anti-inflammatory, blood purifier, antioncogenic, anti-proliferative and hemostatic properties attributed to bioactive phytoconstituents. Oestrogen is the main reason for the increase in the thickness of the endometrium leading to endometrial hyperplasia. *Geru* contains calcium that helps to maintain the hemostatic mechanism.[12] Gulnar (*Punica granatum*) possess strong anti-oestrogenic, anti-inflammatory and antioncogenic activities.[18]According to Kim et al., polyphenols from aqueous pericarp extract can suppress the activity of 17--hydroxysteroid dehydrogenase. Polyphenols from the pericarp of pomegranate juice reduced the growth of ER+ MCF-7 and ER- MB-MDA-231 breast cancer cell lines in terms of anti-estrogenic actions. [19] According to new research, ellagic acid may have both estrogenic and anti-estrogenic effects depending on the oestrogen receptor to which it binds. [20]*Sambhalu* (*Vitex negundo* Linn) possess anti-inflammatory and anti-oestrogenic properties.[21]*Mazu* (*Quercus infectoria*) possess a high concentration of tannins (50-70%) and is used for the treatment of menorrhagia.[22] Murdarsang (Litharge)

possesses astringent and anti-inflammatory properties.[23]

Various studies have steadily confirmed the importance of oestrogens in regulating endometrial cell proliferation, angiogenesis and inflammation.[24] The endometrium includes a balanced cytokine system with various linkages during the proliferative and secretory stages of the menstrual cycle. Although inflammation is the most frequent feature in most hyperplasia situations, some research has concentrated on the involvement of various pro- and anti-inflammatory cytokines in EH development. EH was related to "*reduced production of tumour necrosis factor-α (TNF-α), proliferating cell nuclear antigen, and epithelial growth factor mRNA and enhanced production of Fas mRNA"*. Also, TNF- was also shown to be expressed in normal endometrium as well as simple and complicated hyperplasia, while it was downregulated in atypical hyperplasia and endometrial ca. The transcription factor nuclear factor-κB was also found in proliferative endometrium and EH. [1] This shows that anti-inflammatory herbs may have the potential to treat EH and thereby regularize menstruation. Table 7 summarizes that most of the ingredients of both groups have anti-inflammatory properties. Soy isoflavonoids are well-known inhibitors of protein-tyrosine kinases and topoisomerase-II. [25] Isoflavonoid can be found in genistein. Through cytokine and ER-mediated mechanisms, genistein inhibits the internal cytokines IL-1 α and TNF- α.[26] Likewise herbal medicine that contains isoflavonoids are beneficial in suppressing inflammation. Tannins in *Mazo* possess anti-inflammatory potential, which is positively related to their antioxidant activities. Tannins in experimental studies modulate the inflammatory cytokine release and inhibit the production of nitric oxide (NO) and prostaglandins. Besides *Mazo* also possesses anti-proliferative effects in vitro conditions. [22]

Numerous authors have documented the link between inflammation and oxidative stress. Evidence indicates that oxidative stress plays a pathogenic role in chronic inflammatory diseases. [27] Antioxidants have anti-inflammatory actions that limit nociceptor activity and reduce the production and/or release of prostaglandins that act as inflammatory pain mediators. By blocking the NF-kB pathway, a substance can exhibit both antioxidant and anti-inflammatory characteristics. [28] Plants metabolites such as tannin have anti-inflammatory, haemostatic analgesic, and effects. [29] Flavonoids have anti-inflammatory, antioxidant, and analgesic effects [29]. Flavonoids can scavenge lipid peroxyl radicals, superoxide anion radicals and hydroxyl radicals, and play a key role in preventing illnesses caused by oxidative damage to membranes, proteins and DNA. Saponins and alkaloids have anti-inflammatory properties. Anti-inflammatory activity aids from anti-oxidant characteristics.[30] Polyphenols also have numerous biological activities. Before cell viability is seriously affected, phenolic compounds and flavonoids can interact with ROS/RNS and thus terminate the chain reaction.

Currently, research has established that alum has antihemorrhagic, anti-inflammatory, and antimicrobial properties. Alum is documented to inhibit inflammation via several mechanisms, and its effects include immune cell function inhibition (reduction in lymphocyte infiltration, decrease in dilation, blood vessel congestion and inhibition of goblet cell proliferation). [31] Hence, this study validates that both group Unani regimens were beneficial in abnormal uterine bleeding due to endometrial hyperplasia.

The research Unani medicines reduced excessive menstrual bleeding, reduced inflammation and reduced the thickness of hyperplastic endometrium. As a result of the aforementioned features, both groups were equally effective.

Strengths of the study: This is the first kind of study that evaluated the effectiveness of Holistic Unani therapy in abnormal uterine bleeding due to endometrial hyperplasia. Besides, it was a randomized, parallel

comparative study and no adverse effects were reported.

Limitations and recommendations: The limitations include no follow-up assessment after treatment and no assessment of progression to uterine cancer. A double-blind study could not be carried out due to a lack of facilities, equipment, resources, and staff. To evaluate the efficacy of trial medications on endometrial hyperplasia, additional phase II and III studies, double-blind, placebo/standard controlled with longer treatment duration and follow-ups are needed. The purpose of this study was to validate the efficacy and safety of the Unani formulations in abnormal uterine bleeding. The authors also suggest conducting standardization and quantitative analysis of Unani formulations as well as stability evaluation of the finished product. Furthermore, they recommend checking the presence of active constituents in the bloodstream to assess their absorption and safety. Therefore, comprehensive pharmacokinetics and pharmacodynamics studies are recommended. Furthermore, research is required to determine the precise mechanism of action of these Unani compositions and qualitative analysis of the formulations.

Table 7. Ethnomedicinal, pharmacological and bioactive constituents of the Unani medicine of both groups

Group A Name of compound formulation	**Ethnomedicinal actions**	**Pharmacological activities**	**Bioactive constituents**	**Ref.**
Itrifal Aftimoon	*Amrade Dimagh* Purifies blood and cleans the body from humour, Antiphlegmatic purgative, Carminative, Refrigerant.	Anti-inflammatory, anti-inflammatory, antioxidant, astringent, demulcent	Steroids, alkaloids, flavonoids, saponins Tannins Anethole, ellagic acid, bellaricanin, Beta-sitosterol, quercetin, resins, cuscutin, inorganic compounds-calcium, iron, magnesium, potassium and tin	[15,32–34]
Marham Dakhilyun	Local astringent, anti-phlegmatic, relieves pain from inflamed parts, carminative, refrigerant	Wound healing, anti-inflammatory, antioxidant, antibacterial, immunomodulatory, hepatoprotective neuroprotective anticancer, powerful local astringent, Haemostatic	Flavonoids, iridoids, flavanones, biophenols, triterpenes, isochromans, steroidal saponins, alkaloids, phenols, and polysaccharides flavonoids, lignans, vitamins E and C,	[35,36]

Group B Unani Name	**Botanical Name**	**Ethnomedicinal Actions**	**Pharmacological Activities**	**Bioactive Constituents**	**Ref.**
Gulnar Farsi	*Punica granatum*	Astringent, antidysenteric, dessicant	Antioxidant, antimicrobial, antioncogenic, anti-inflammatory, antibacterial, antiviral, antitumour, anti oestrogenic	Tannins, Saponins, Organic acids, flavonoids, alkaloids	[37]
Geru	Rubra red earth (silicate of aluminia and oxide of Fe (Haemalite)	Astringent, cooling, resolvent, haemostatic anti- inflammatory	Astringent, anti-phlegmatic, anti-bilious and cooling	Calcium	[12, 38]
Phitakri Biryan	Alum	Astringent caustic haemostatic antispasmodic	Antihemorrhagic, anti-inflammatory, and antimicrobial, analgesic,	Potassium, aluminium, sulphur, oxygen	[39–41]

			antioxidant, antibiotic, enhances antibody responses to stimulate innate immunity, astringent, antitumour		
Dammul Aqwain	*Dracaena cinnabari* Balf.f.	Astringent, haemostatic, antidiarrhea, carminative	Wound healing, anti-inflammatory, analgesic, antimicrobial, antidiabetic, antispasmodic, relaxant, anticancer, antitumour	Tannin, drocoresinotannols, dracorsen and flavone quinones, triflavonoids sterols, triterprnoids, dracidione	[42]
Bargh Sambhalu	*Vitex negundo* Linn.	Astringent, demulcent, resolvent	Antioxidant, chemopreventive, immunomodulatory and cytotoxicity, antimicrobial, antifungal, antinociceptive, opioidergic, anti-estrogenic, anti-inflammatory	Flavonoid Casticin, phenols, tannin, α-pinene, limonene, β-caryophyllene, sabinene, and β-farnesene	[43]
Mazu	*Quercus infectoria*	Astringent, Hemosyptic,	Anti-inflammatory, anti-oxidant, anti-proliferative	Tannin, gallic Acid, tannic acid, flavonoids, polyphenols, steroids, terpenoids, saponins, glycosides	[22]
Kalijiri	*Centratherum anthelminticum*	Diuretic, stomachic, anthelmintic	Smooth muscle relaxant, hypotensive,	Delta 7- avenasterol, flavones, saponins, steroids, glycosides	[14,44]
Both groups					
Roghan Gul	*Rosa damascene* oil	Astringent, tonic, anti-inflammatory	Anti-inflammatory, anti-microbial, antioxidant, antitussive, hypnotic, antidiabetic, relaxant, anti-mutagenic	terpenes, glycosides, flavonoids, anthocyanins, vitamin C, kaempferol, quercetin	[32, 45,46]

Conclusion

This study reveals that Group A and B were equally beneficial in the treatment of abnormal uterine bleeding due to endometrial hyperplasia as research medicines regularized abnormal uterine bleeding and normalized endometrial thickness by their anti-inflammatory, anti-proliferative and astringent properties. Furthermore, experiments comparing the efficacy of both groups with conventional control are recommended.

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