

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

Abothu Suhasini^{1*}, Wasia Naveed², Arshiya sultana^{3*}, Shahzadi Sultana⁴

¹Professor, Department of *Ilmul Qabalat wa Amraze Niswan (Gynaecology and Obstetrics)*, Govt. Nizamia Tibbi College, Hyderabad, Telangana.

²Department of *Ilmul Qabalat wa Amraze Niswan (Gynaecology and Obstetrics)*, Govt. Nizamia Tibbi College, Hyderabad, Telangana.

³Professor, Department of *Ilmul Qabalat wa Amraze Niswan (Gynaecology and Obstetrics)*, National Institute of Unani Medicine, Ministry of AYUSH, GOI, Bengaluru 560091, Karnataka, India

⁴In-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 Biryani* (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 *Hamul 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.

¹Abnormal uterine bleeding (AUB) refers to any form of

*Correspondence: Abothu Suhasini, Arshiya sultana
E-mail: drasahasini@yahoo.com; drarshiya@yahoo.com
Received Oct 06, 2023; Accepted Nov 22, 2023; Published Nov 30, 2023
doi: <http://dx.doi.org/10.5667/CellMed.2023.019>

©2023 by CellMed Orthocellular Medicine Pharmaceutical Association

This is an open access article under the CC BY-NC license.
(<http://creativecommons.org/licenses/by-nc/3.0/>)

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

bleeding that does not fall within the usual parameters for frequency, amount, duration, or cyclicity. 20% of 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 mellitus, PCOS, smoking, obesity, nulliparity, late onset of menopause⁴ 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 *Hārr* 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 Hārr* 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 Biryani*, *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

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

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 *Hamul* of *Marham Dakhilyun* (5g) and *Roghan Gul* (10ml) advised for 10 days from day 5 of menses. Table

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

1 Summarizes the ingredients of *Itrifal Aftimoon* and *Marham Dakhilyun*.

Group B: Medicine included in group B were powder of *Gulnar Farsi*, *Phitakri Biryani*, *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 Biryani* (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 *Hamul* 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* Ointment⁸

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

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

7.	<i>Tukhme Hulba</i>	<i>Trigonella foenum-graecum L.</i>	20
8.	<i>Mom Zard</i>	Bee Wax	Quantity required

Results

various reasons. Then, 40 patients were assigned to groups A and B at random (**Figure 1**).

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

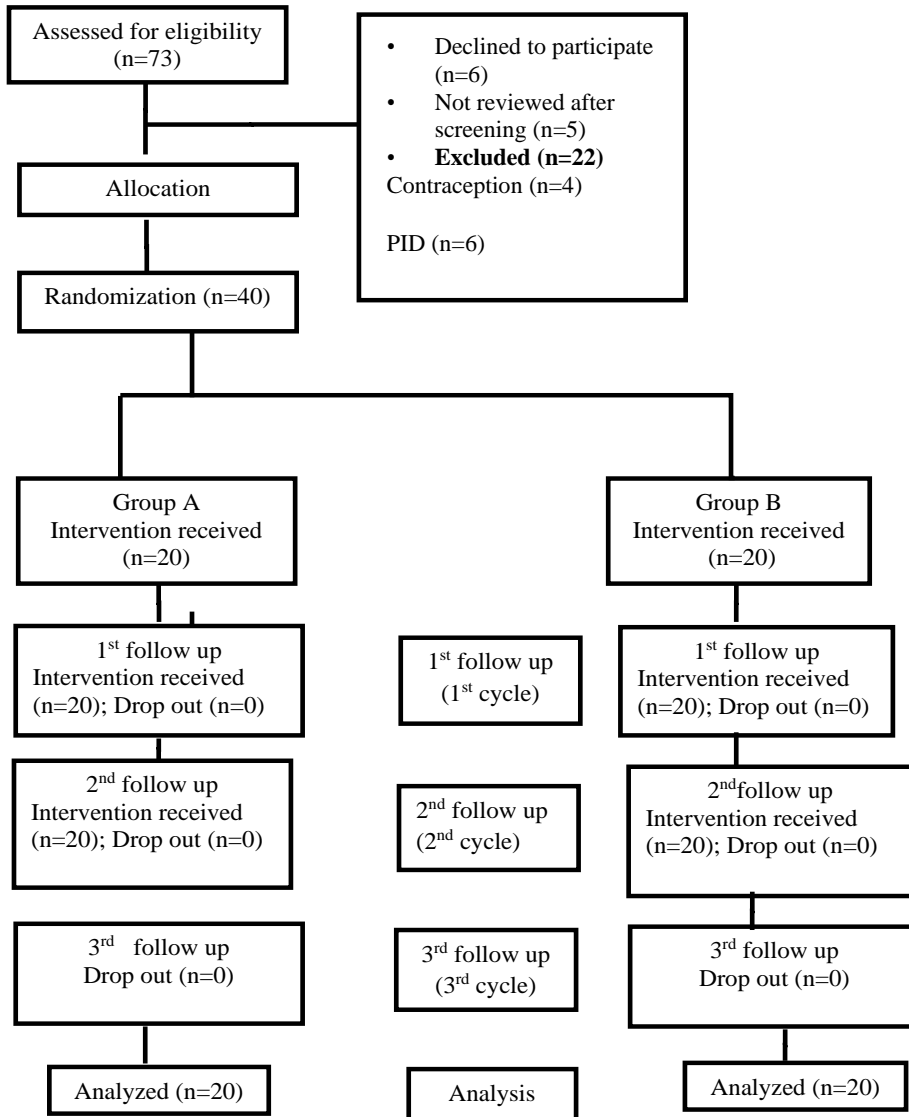


Fig 1: Flow Chart of participants as per Consort statement

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

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	16	80	16	80	32	80	1.00 ^b
Anteverted							
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	

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

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

Test used: ^bChi-square; ^aFisher 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)	%	Group B (n=20)	%
	No of patients		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)	Group B (n=20)	P value
	No of patients	No of patients	
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			
	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

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

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 Biryani*, *Dammul Aqwain*, *Geru*, *Bargh Sambhalu*, *Mazu*, *Kaljiri*, 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 Biryani*¹² which helps in haemostasis. Moreover, *Kathrat-i-Hayd* is triggered by *Du'f Quwwat Māsika* (weak retentive power) and *Qāwi 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*.¹²¹³ 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*)

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

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- κ B 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- κ B 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 effects²⁹. Flavonoids can scavenge lipid peroxy 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

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

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.	
<i>Itrifal Aftimoon</i>	<i>Amrade Dimagh</i> 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	
<i>Marham Dakhilyun</i>	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.
<i>Gulnar Farsi</i>	<i>Punica granatum</i>	Astringent, antidiysenteric, dessicant	Antioxidant, antimicrobial, antioncogenic, anti-inflammatory, antibacterial, antiviral, antitumour, anti oestrogenic	Tannins, Saponins, Organic acids, flavonoids, alkaloids	37
<i>Geru</i>	Rubra red earth (silicate of alumina and oxide of Fe (Haemalite)	Astringent, cooling, resolvent, haemostatic anti-inflammatory	Astringent, anti-phlegmatic, anti-bilious and cooling	Calcium	12, 38
<i>Phitakri Biryani</i>	Alum	Astringent caustic haemostatic antispasmodic	Antihemorrhagic, anti-inflammatory, and antimicrobial, analgesic,	Potassium, aluminium, sulphur, oxygen	39-41

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

			antioxidant, antibiotic, enhances antibody responses to stimulate innate immunity, astringent, antitumour		
<i>Dammul Aqwain</i>	<i>Dracaena cinnabari</i> 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, triterpenoids, dracidione	42
<i>Bargh Sambhalu</i>	<i>Vitex negundo</i> 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
<i>Mazu</i>	<i>Quercus infectoria</i>	Astringent, Hemosyptic,	Anti-inflammatory, anti-oxidant, anti-proliferative	Tannin, gallic Acid, tannic acid, flavonoids, polyphenols, steroids, terpenoids, saponins, glycosides	22
<i>Kalijiri</i>	<i>Centratherum anthelminticum</i>	Diuretic, stomachic, anthelmintic	Smooth muscle relaxant, hypotensive,	Delta 7- avenasterol, flavones, saponins, steroids, glycosides	14,44
Both groups					
<i>Roghan Gul</i>	<i>Rosa damascene</i> oil	Astringent, tonic, anti-inflammatory	Anti-inflammatory, antimicrobial, 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.

Acknowledgement: The authors are thankful to the patients and staff of Govt. Nizamia Tibbi College for their support in carrying out this work.

Conflict of interest: Nil

Funding: Nil

References

1. Chandra V, Kim JJ, Benbrook DM, Dwivedi A, Rai R. Therapeutic options for management of endometrial hyperplasia. *J Gynecol Oncol* **27**, 1–25 (2016).
2. Sajitha K, Padma SK, K JS, HI KP, Permi HS, Hegde P. Study of histopathological patterns of endometrium in abnormal uterine bleeding. *CHRISMED J Heal Res* **1**, 76–81 (2014).
3. Goldstein SR. Menorrhagia and abnormal bleeding before the menopause. *Best Pract Res Clin Obs Gynecol* **18**, 59–69 (2004).
4. Sanderson PA, Critchley HOD, Williams ARW, Arends MJ, Saunders PTK. New concepts for an

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

- old problem: the diagnosis of endometrial hyperplasia. *Hum Reprod Update* **23**, 232–54 (2017).
5. Preethi RKS. Analysis of clinical and histomorphological features of endometrium in abnormal uterine bleeding- e with special stain application. Dr MGR Medical University [Dissertation]; 2020.
 6. Khan A. *Iksir-i-A'zam*. (Idarae Kitabus Shifa: New Delhi, 2011) 781–6 p.
 7. Qarshi M. *Jamu al-Hikmat*. (Idarae Kitabus Shifa New Delhi, 2011) 1121–23 p.
 8. Anonymous. *Govt. Unani Pharmacopoeia*. (Govt. Central Press: Andhra Pradesh, 1988) 62, 64 p.
 9. Ghani, N. Khazainul Advia. (Idarae Kitabus Shifa New Delhi, YNM) 999–1002 p.
 10. Giri SK, Nayak BL, Mohapatra J. Thickened Endometrium : When to Intervene ? A Clinical Conundrum. *J Obstet Gynecol India* **71**, 216–25 (2021).
 11. Fraser, I. S.; Mc Carron G. Randomized trial of 2 hormonal and 2 prostaglandin- inhibiting agents in women with a complaint of menorrhagia. *Aust N Z J Obs Gynaecol* (1991) 31(1):66–70.
 12. Fathima A, Sultana A. Clinical efficacy of a Unani formulation “Safoof Habis” in menorrhagia: A randomized controlled trial. *Eur J Integr Med* **4**, (2012).
 13. Sina I. *Al-Qanun fi'l Tibb*. (Idarae Kitabus Shifa New Delhi, 2010) 1095 p.
 14. Khare CP. *Indian Medicinal Plants: An Illustrated Dictionary* (Google eBook [Internet]. (Springer:Berlin Heidelberg 2007). 900 p. Available from: <http://books.google.com/books?id=gMwLwbUwtfkC&pgis=1>
 15. Nadkarni KM. *Indian plants and drugs*. (Srishti Book Distributors: New Delhi, 2004). 9,10,11,311,312 p.
 16. Kirtikar and Basu B. *Indian Medicinal Plants*. Vol I. 2nd ed. (International Book Distributors Dehradun, 2012) 1289–92 p.
 17. De Jesus NZ, Falcão HS, Gomes, IF, Leite TJA, LG, Barbosa-Filho JM, Tavares JF, Silva MS AF, PF BL. Tannins, peptic ulcers and related mechanisms. *Int J Mol Sci* **13**, 3203–28 (2012).
 18. Mandal A, Bhatia D, Bishayee A. Anti-Inflammatory mechanism involved in pomegranate-mediated prevention of breast cancer. *Nutrients* **436**, 1–13 (2017).
 19. Kim ND, Mehta R, Yu W, Neeman I, Livney T, Poirier D, et al. Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer. *Breast Cancer Res Treat* **71**, 203–17 (2002).
 20. Sturgeon, S.R.; Ronnenberg AG. Pomegranate and breast cancer: Possible mechanisms of prevention. *Nutr Rev* **68**, 122–128 (2010).
 21. Jivrajani M, Ravat N, Anandjiwala S, Nivsarkar M. Antiestrogenic and anti-inflammatory potential of n -hexane fraction of *Vitex negundo* linn leaf extract : a probable mechanism for blastocyst implantation failure in *Mus musculus*. *International Scholarly Research Notices* 2014 (2014).
 22. Mahboubi M. *Quercus infectoria* fruit hulls and galls and female genital disorders. *Clin*

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

- Phytoscience* **6**, 1–6 (2020).
23. Sultana Arshiya; Rahman Khaleequr; MUZN Farzana\; Mudarsang (Plumbi oxidum): A Mineral with medicinal properties. *Ayurveda Sameekshawa* **2**, 11–5 (2013).
24. Gibson DA SP. Estrogen dependent signaling in reproductive tissues - a role for estrogen receptors and estrogen related receptors. *Mol Cell Endocrinol* **348**, 361–372 (2012).
25. Yamashita Y, Kawada S NH. Induction of mammalian topoisomerase II dependent DNA cleavage by nonintercalative flavonoids, genistein and orobol. *Biochem Pharmacol* **39**,737–44 (1990).
26. Lian Z, Niwa K, Tagami K, Hashimoto M, Gao J, Yokoyama Y et al. Preventive effects of isoflavones, genistein and daidzein, on estradiol-17 beta-related endometrial carcinogenesis in mice. *Jpn J Cancer Res* **92**, 726–34 (2001).
27. Hussain T, Murtaza G, Metwally E, Kalhoro DH, Kalhoro MS, Rahu BA, et al. The role of oxidative stress and antioxidant balance in pregnancy. *Mediators Inflamm* 2021, (2021).
28. Agnieszka, G, Skrzydlewska E. Antioxidative and anti-inflammatory activity of ascorbic acid. *Antioxidants* **11**, (2022).
29. Safari VZ, Kamau JK, Nthiga PM, Ngugi MP, Orinda G, Njagi EM. Antipyretic, antiinflammatory and antinociceptive activities of aqueous bark extract of *Acacia nilotica* (L.) Delile in Albino Mice. *J Pain Manag Med* **02**, (2016).
30. Abdulhamid A, Sani I, Kankiya IH, Fakai IM. Phytochemical Screening, Analgesic effect and anti-inflammatory activity of crude methanolic stem bark extract of *Acacia nilotica* (Linn.). *Asian J Biol Sci* **12**, 450–6 (2019).
31. Baria AH, Patel RP, Suthar AM PR. Formulation development and evaluation of sustained release aceclofenac suppository. *Int J Pharm Sci Drug Res* **1**, 71–3 (2009).
32. Ansari S, Zeenat F, Ahmad W, Ahmad I, Syed Ziaul Hasan Govt H. Therapeutics and pharmacology of Gul-e-Surkh (*Rosa damascena* Mill): An important Unani drug. *Int J Adv Pharm Med Bioallied Sci* **5**, 195–205 (2017).
33. Afrin Z, Siddiqui A, Jafri MA, Vohora D, Asif M. Preliminary screening of a classical unani formulation Majoon Najah for anticonvulsant activity. *Int J Pharm Res* **11**, 142–53 (2019)
34. Bansod M. Vitex negundo L : Phytochemical constituents , traditional uses and pharmacological properties: Comprehensive Review *Pharmacologyonline* 1: 286-302 (2009) Newsletter Bansod and Harle. 2016;(January 2009).
35. Bonaterra GA, Bronischewski K, Hunold P, Schwarzbach H, Heinrich EU, Fink C, et al. Anti-inflammatory and Anti-oxidative Effects of Phytostil® and Root Extract of *Althaea officinalis* L. on Macrophages in vitro. *Front Pharmacol* **11**, 1–14 (2020).
36. Al-Snafi AE. The Pharmaceutical importance of *Althaea officinalis* and *Althaea rosea*: A review. *Int J PharmTech Res* **5**, 1378–85 (2013).
37. Shaygannia E, Bahmani M, Zamanzad B, Rafeian-Kopaei M. A review study on *Punica granatum* L. *J Evid Based Complementary Altern Med* **21**, 2016

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

38. Kotagasti T. Efficacy of Geru (red ochre) in controlling the bleeding in patients of adolescent menorrhagia. *TANG [Humanitas Med]* 5, 12.1-12.3. (2015). (Menorrhagia). *J Int Soc Hist Islam Med (JISHIM)* (2011-2012).
39. Bartels DA, Johnson R, Bayor MT, Ainooson GK, Ossei PPS, Etuaful RK, et al. Formulation of Suppositories of Alum Produced from Bauxite Waste in Ghana for the Treatment of Hemorrhoid. *Sci World J* 2021; 2021.
40. Seo H sik. An Experimental Study of the Anti-oxidant and the anti-inflammatory effects of alumand burnt alum. *J Pharmacopuncture* 15, 11–4 (2012).
41. Wen Y, Shi Y. Alum: an old dog with new tricks. *Emerg Microbes Infect* 5, 1–5 (2016).
42. Al-Fatimi M. Ethnobotanical survey of *Dracaena cinnabari* and investigation of the pharmacognostical properties, antifungal and antioxidant activity of its resin. *Plants* 7, 1–13 (2018).
43. Naveed W, Shameem I, Tabassum K. Clinical Study of mutlazima qabl haiz (premenstrual syndrome) and its management with Unani formulation - a randomized controlled trial. *Int J Cur Res Rev* 6, 51–7 (2014).
44. Forouzanfar F, Fazly Bazzaz BS, Hosseinzadeh H. Black cumin (*Nigella sativa*) and its constituent (thymoquinone): A review on antimicrobial effects. *Iran J Basic Med Sci* 17, 929–38 (2014).
45. Boskabady MH, Shafei MN, Saberi Z, Amini S. Pharmacological effects of *Rosa damascena*. *Iran J Basic Med Sci* 14, 295–37 (2011).
46. Sultana A, Rahman K, Begum M, Rahman S. Views of Ibn Sina (Avicenna) on ifraat haiz