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Effect of *Muqil, Murmakki, Abhal*in Polycystic Ovarian Disease associated Secondary Amenorrhoea: An observational study

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Abstract
Background and objectives: *Amenorrhoea is not a diagnosis in itself, but rather a most common clinical sign of reproductive dysfunction and the incidence of amenorrhoea due to polycystic ovarian syndrome is 28%. The objective of the study was to evaluate the efficacy and safety of research drugs Muqil, (Commiphoramuqul), Murmakki (Commiphoramyrrha) and Abhal (Juniperuscommunis*Linn*) in Polycystic Ovarian Disease (PCOD) associated Secondary Amenorrhoea.*
Methods: *A single blind non-randomized pre and post observational study was carried out at National Institute of Unani Medicine Hospital, Bengaluru. Patients (n=30) with PCOD in the age group of 18-35 years with oligo/secondary amenorrhoea were included in the study.Patients with thyroid dysfunction, hyperprolactinemia, systemic illnesses, malignancies, use of hormonal pills in last 2 months, pregnancy and lactation were excluded. Research drugs were administered orally in a dose of 6 g/day (tablet form) with water for seven days in a month for three consecutive months. Primary outcome measure (withdrawal bleeding) and secondary outcome measure (menstrual regulation) were assessed to determine the effect of research drugs. Data were analyzed using paired Student's t-test.*
Results: *Withdrawal bleeding was achieved in 63.33% patients, while 36.6% patients had no bleeding. Menstrual regulation was achieved in 73.33% patients; where as 26.66% had persistent irregular menstruation. Achievement in outcome measures is due to improvement in duration of cycle, which though increased in 1st cycle of treatment (P<0.001), and then decreases in subsequent cycles; highly significant reduction in BMI (P<0.001), suggestive significant change in waist circumference (P=0.064+) and absence of PCOD in 20% of patients was noted after treatment. No significant difference in hirsutism, luteinizing hormone/follicle stimulating hormone ratio and mean ovarian volume was observed during the trial.*
Interpretation and conclusion: *Research drugs (Muqil, Murmakki, Abhal) was an effective alternate therapeutic option in patients with PCOD associated secondary amenorrhoea.*
Keywords: *PCOD; Secondary Amenorrhoea; Muqil; Murmakki; Abhal; Withdrawal Bleeding; Menstrual Regulation.*

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I. Introduction

Secondary amenorrhoea occurs in 10-20% of patients complaining of infertility and is one of the commonest reasons for referral to a gynaecological endocrine clinic.[1,2] Amenorrhoea is not a diagnosis in itself but rather a most common clinical sign of reproductive dysfunction.[1,3]It is caused by many pathological states, including polycystic ovarian syndrome (PCOS), Cushing's syndrome, hypopituitarism, hypothyroidism, and hyperprolactinemia.[2,3] Evaluation and management of a patient with amenorrhoea is a common practice in gynaecology and the prevalence of pathologic amenorrhoea ranges from 3-4% in reproductive aged population.[2,3,4,5] and the incidence of amenorrhoea due to polycystic ovarian syndrome is 28%.[3]PCOS is a heterogeneous disorder, with multiple reproductive, cosmetic and metabolic complexities[6] which is characterized by dysfunction in ovulation and clinical or biochemical hyperandrogenism and the presence of polycystic ovarian morphology.[7,8]Pathophysiology of PCOS is a complex process, obesity and insulin resistance plays a major role in its causal.[9] Women with PCOS have increased rate of insulin resistance as well as hyperandrogenism which have been implicated in the dysfunction of HPO-axis, leading to anovulation and menstrual irregularities.[7,10] Women with amenorrhoea are at increased risk of developing endometrial hyperplasia from chronic unopposed estrogen.[1]

In classical Unani text, it is mentioned that *ihtibas-i-tams* (amenorrhoea) usually occurs in women with *balghamimizaj*(phlegmatic temperament) and fair complexion,[11]and is mainly caused by dominance of *khilt-i-balgham*(phlegm) which increases the viscosity of *khun-i-hayd*(menstrual blood) and form *sudda*(obstruction), as a result menstrual blood fails to expelled out of the uterus.[11-13]Even, abnormal production of *balgham* causes *zo'af-i-*

jigar(liver dysfunction) which leads to *ihtibas-i-tams* and this abnormal *balgham*gets accumulated in sac to form cyst in ovaries.[14,15]Any disturbance in menstrual regularity is abnormal and may lead to consequences like obesity, infertility, virilization, hysteria, leucorrhoea, ascites, uterine cancer, psychological stress etc.[3,11-13]

The prognosis depends on the cause of amenorrhoea. Secondary amenorrhoea associated with PCOD will respond to treatment.[1] The available treatment in conventional medicine is hormone therapy (for withdrawal bleeding and menstrual regulation) and also use of insulin sensitizing agents (to reduce insulin resistance and androgen levels as well as to improve ovulatory function) in women with PCOS.[10] Metformin, the most widely used drug in PCOS is often poorly tolerated because of gastrointestinal side effects,[7,10] and hormonal therapy though effective in menstrual cyclicity, has got its own complications like venous thrombo-embolism, stroke, breast, endometrial and ovarian cancer and are contraindicated in patients with hypertension, cardiac diseases, liver diseases, DVT etc.[1]Conventional pharmaceutical management is limited by the prevalence of contraindications in women with PCOS, non-effectiveness in some circumstances, side effects and by preferences of women with PCOS for alternatives to pharmaceutical management.[7,17]Hence due to side effects, contraindications and complications, there is an increase demand for herbal therapy which is to be safe, effective and easily available.

The treatment plan inUnani system of medicine for secondary amenorrhoea in PCOD patients is based on the concept that, treat the cause of amenorrhoea i.e. PCOD with life style modification through *tadbir* (regimental therapy), *ghiza* (diet), *dawa* (medicines);[11] use of *qawimudirr-i-haydadvia* (strong emmenogogue drugs)[12] to induce menstruation; use of *munzij* (coctive) *wamushil-i-balghamadvia* (purgative) drugs for *tanqia-i-badan* (detoxification of the body)[11] and finally use of Unani medicine which act as insulin sensitizers.[14]

Several single drugs and compound formulations are enlisted in the management of secondary amenorrhoea in PCOD patients. Drugs such as*Muqil (Commiphoramukul), Murmakki (Commiphoramyrrha,)* and *Abhal (Juniperuscommunis*Linn.*)*[13,17]was selected as research drugs to induce menstruation in PCOD patients, as they exhibit the properties of *mudirr-i-bawl wahayd* (diuretic and emmenogogue),*mufattit-i-sudad* (de-obstruent),*mulattifkhun* (anti-thrombotic), *muharrik* (stimulant),*muqawwi-i-jigar* (liver tonic),*mujaffif* (dessicant)*muhallil-i-waram*(anti-inflammatory),*munaffiswamukhrij-i-balgham*(expectorant),*mushil*(purgative) etc.[13,17-19]Moreover, pharmacological studies suggest that *Muqil*, *Mur*and *Abhal* possess hypoglycemic,[20,21]hypolipidemic,antithrombotic,[18,19]antioxidant,[20,21,22]anti-inflammatory,[18,19,21]and stimulant[18,19] activities. Further, these drugs contain steroids and flavonoids, *Mur* contains phytosterol, saponins, terpenoids, lignans, phenolic compounds etc, while *Abhal*contains glycosoids and alkaloids as well,[21,22,23] which probably may induce withdrawal bleeding and regularize the menstruation by reduction in BMI and improving insulin resistance in secondary amenorrhoea associated with PCOD.

The study was designed to test the hypothesis whether *Muqil, Murmakki, Abhal* could induce withdrawal bleeding and menstrual regulation in patients with PCOD associated secondary amenorrhoea and this was the first study with these drug combination. The objective of the study was to determine clinically the efficacy and safety of research drugs (*Muqil, Murmakki, Abhal)* in PCOD associated secondary amenorrhoea.

II. Material and methods

2.1: Study design and setting: A single blinded, non-randomized, pre and post observational study was carried out in Dept. of *IlmulQabalatwaAmrazeNiswan*, National Institute of Unani Medicine Hospital, Bengaluru in a duration of one and half year.

2.2: Subjects and method: 176 patients were screened for the study from OPD and IPD of the Hospital. 30 Patients fulfilling the inclusion criteria were enrolled in the study and written informed consent was obtained. Ethical approval was obtained from the ethical committee of the institute under IEC No: NIUM/IEC/2014-15/011/ANQ/03 after which the clinical study was started.

Detailed history was elicited from each included patient, regarding nature of cycle (regular/irregular), menstrual cycle length, duration and amount of flow, previous treatment received for irregular menstruation and its outcome, and complete physical examination including gynaecological examination (restricted to married women only) was performed in all patients. Height, weight, BMI, waist circumference, hirsutism score and vitals were noted along with assessment of socioeconomic status, *mizaj* (temperament), menstrual blood loss was also recorded in case record form designed for the study.

2.3: Sample size calculation: Sample size was determined on the basis of previous study conducted on PCOS women meeting the Rotterdam criteria with improvement in menstrual cyclicity from baseline (+0.23 cycles/month, 95% confidence interval, 0.099-0.36) in 6 months intervention; powered to detect a 40% increase in menstrual cycle frequency with a type II error of 0.20 and a type I error of 0.05, the target sample size of 45 was calculated.[10]However, due to time constraint, practical feasibility and availability of patients in hospital, the sample size of 30 was kept as single group.

2.4: Selection Criteria of patients:

Inclusion criteria: Patients in the age group of 18-35 yearswho had menstrual irregularities like oligomenorrhoea,amenorrhoeawith PCOD.

Exclusion criteria: Pregnant and lactating women and patients who had thyroid dysfunction, hyperprolactinemia, systemic illnesses, malignancy and those on hormonal pills in last 2 months .

2.5: Intervention: All crude drugs (*Muqil, Murmakki, Abhal*) were taken in equal quantity; cleaned, finely powdered and tablets were prepared; one tablet was approximately of 750 mg and three tablets was administered orally thrice dailyto fulfill the dose of 6 g/day with water for 7 days in a month for three cycles.

Fig. 1. *Mukil, Murmakki, Abhal* (Research drugs)

2.6: Parameters for evaluation of efficacy of test drug:

Subjective parameters: During first cycle of treatment, withdrawal bleeding was assessed with nature of cycle, duration of cycle, duration of flow and amount of flow (PBAC score) and even change in bodyweight was assessed with calculation of BMI.

Objective parameters: Body Mass Index, waist circumference, hirsutism, and investigations such as pelvic scan, Sr. LH/FSH ratio was performed during the trial. The statistical analysis of these findings was done as pre and post treatment and presented in the form of tables.

2.7: Follow up: All the patients who were studied under this clinical trial, after completion of treatment for prescribed period were instructed to have regular follow up at an interval of one month for a period of 3 months. During this follow up study period, patients were questioned for the regularity of menses.

2.8: Assessment of efficacy:

Primary outcome measure: Withdrawal bleeding during first treatment cycle.

Secondary outcome measure: Menstrual regulation in subsequent cycles of treatment.

2.9: Statistical analysis: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale within each group.Significance is assessed at 5% level of significance. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data.

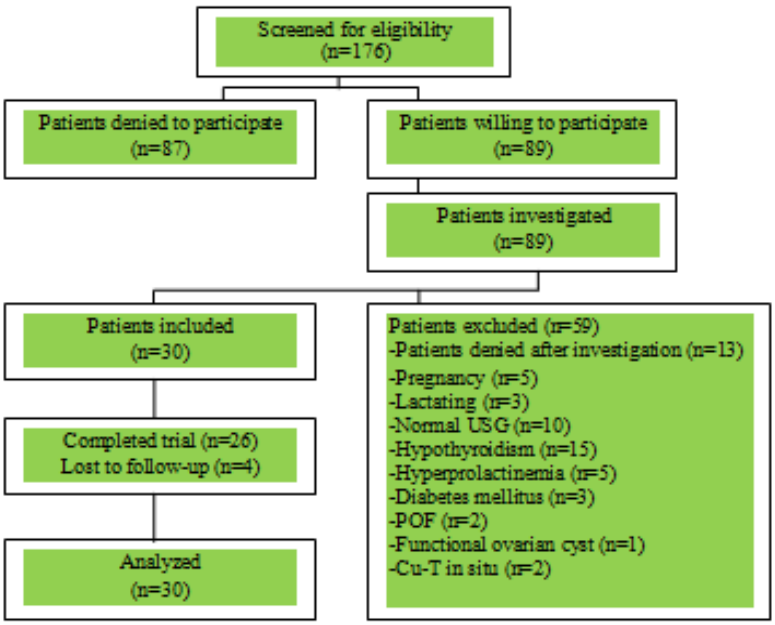

Fig. 2.Study flow chart

III. Result

A total of 176 patients were screened for the study, 87 patients declined to participate and 89 were evaluated through investigations; 59 patients were excluded for not meeting the inclusion criteria, and 30 patients were

enrolled in the study. 26 patients completed the 3 months of intervention, 1 patient got pregnant after 3rd cycle of treatment and 4 patients were lost to follow up and not visited again for posttest and the same were included in the analysis by last observation carry forward method**.**

Table no-1: Demographic Data

Demographic data	Results
Mean Age (years)	27.53±4.83
Socioeconomic status • Upper • Upper middle • Upper lower • Lower middle	 3 (10%) 11 (36.7%) 6 (20.0%) 10 (33.3%)
Marital status • Married • Unmarried	 25 (83.3%) 5 (16.7%)
Mean age of Menarche	13.2±1.92
Mizaj • *Damwi* • *Balghami* • *Safrawi* • *Sawdawi*	 10 (33.3%) 14 (46.7%) 1 (3.3%) 5 (16.7%)
Acne • Negative • Positive	 18 (60.0%) 12 (40.0%)
Acanthosisnigrican • Negative • Positive	 8 (26.7%) 22 (73.3%)

Data were presented as mean ±SD and number (percentage), Student's t-test (two tailed, dependent)

Subjective parameters

Table No-2 (a): Effect of Research Drugs on Nature of cycle

Nature of cycle	Before treatment	During treatment			After treatment
		1st cycle	2nd cycle	3rd cycle	
Irregular	30(100%)	-	2(6.7%)	2(6.7%)	6(20.0%)
Regular	-	-	17(56.7%)	22(73.3%)	20(66.7%)
WDB	-	19(63.3%)	6(20.0%)	4(13.3%)	-
No WDB	-	10(33.3%)	-	-	-
PA	-	1(3.3%)	5(16.7%)	2(6.7%)	3(10.0%)
Total	30(100%)	30(100%)	30(100%)	30(100%)	29(96.66%)*

Data were presented as number (percentage)*1 patient conceived, Student's t-test (two tailed, dependent), WDB-withdrawal bleeding, PA-persistent amenorrhoea

Table No-2 (b): Effect of Research Drugs on Duration of cycle, Duration of flow & Amount of flow

Subjective parameters	Before treatment	During treatment			After treatment
		1st cycle	2nd cycle	3rd cycle	
Duration of cycle (Days)	49.17±32.71	90.17±30.82 (P<0.001**)	64.45±47.14 (P=0.149)	55.43±50.14 (P=0.492)	45.07±43.62 (P=0.594)
Duration of flow(Days)	4.37±1.54	2.79±2.53 (P=0.007**)	4.52±2.00 (P=0.880)	4.11±1.45 (P=0.216)	4.73±2.51 (P=0.620)
Amount of flow (PBAC)	94.03±63.65	50.53±59.38 (P=0.004**)	87.90±82.06 (P=0.593)	87.40±57.43 (P=0.500)	103.97±79.99 (P=0.490)

Data were presented as mean ±SD, Student's t-test (two tailed, dependent)** Strongly significant (P value: P≤0.01)

Objective parameters

Table No-3 (a): Effect of Research Drugs on PCOD

PCOD	Before Treatment	After Treatment	% change
Negative	0 (0%)	6(20%)	20%
Positive	30 (100%)	23(76.66%)	-23.34%
Total	30 (100%)	29 (96.66%)*	-

Data were presented as number (percentage), Student's t-test (two tailed, dependent), *1 patient conceived

Table No-3 (b): Effect of Research Drugs on BMI & Waist Circumference

Parameters	Before Treatment	After Treatment	P value
BMI	29.71±3.87	28.89±3.75	P<0.001**
Waist circumference	96.10±6.05	95.43±6.40	0.064+

Data were presented as mean± SD, Student's t-test (two tailed, dependent) + Suggestive significance (P value: 0.05<P<0.10), ** Strongly significant (P value: P≤0.01)

Table No-3 (c): Effect of Research Drugs onHirsutism

Hirsutism (mFG score)	Before treatment	After treatment	% change & P value
<8	21 (70%)	20 (66.6%)	3.4
8	9 (30%)	9 (30%)	0
Total	30 (100%)	29(96.6%)*	-
Mean ±SD	5.93±3.42	6.03±3.43	P>0.05

Data were presented as number percentage and mean± SD, Student's t-test (two tailed, dependent), *1 patient conceived**,** m FG score- Modified FerrimanGallwey Score

Table No-3(d): Effect of Research Drugs on LH/FSH ratio

LH/FSH ratio	Before Treatment	After Treatment	% change& P value
1	3 (10%)	7 (23.3%)	13.3
1-2	18 (60%)	14 (46.6%)	-13.3
>2	9 (30%)	8 (26.6%)	3.4
Total	30 (100%)	29 (96.6%)*	-
Mean ±SD	1.73±0.67	1.72±0.95	0.833-

Data were presented as number percentage and mean± SD, Student's t-test (two tailed, dependent), *1 patient conceived, (P value: 0.01<P ≤ 0.05)

Table No-3 (e): Effect of Research Drugs on Ovarian Volume

Ovarian volume	Before treatment	After treatment	P value
Right ovarian volume	11.85±4.13	10.80±3.77	0.186
Left ovarian volume	12.79±4.39	10.66±4.47	0.030*
Mean ovarian volume	12.32±4.26	10.73±4.12	0.07

Data were presented as mean± SD, Student's -test (two tailed, dependent), *Moderately significant (P value: 0.01<P ≤ 0.05)

Outcome Measures

Table No-4: Effect of Research Drugs on Outcome Measures

Outcome measures	No. of patients (n=30)	%
Withdrawal bleeding		
• No	11	36.67%
• Yes	19	63.33%
Menstrual regulation		
• No	8	26.67%
• yes	22	73.33%

Data were presented as number (percentage), Student's t-test (two tailed, dependent)

IV. Discussion

4.1: Main findings: In the present study, it was observed that withdrawal bleeding was achieved in 63.33% patients, while 36.6% patients had no bleeding. Menstrual regulation was achieved in 73.33% patients, whereas 26. 66% had persistent irregular menstruation. Significant reduction in BMI and waist circumference probably may result in withdrawal bleeding and menstrual regulation which in turn improves the PCOD.

4.2: Demographic data:

Age: Majority of patients (63.3%) was in the age group of 20-30 years, Alnakash AH. *et al*[8] reported 59.81%. Kouser*et al*[24] reported 46.66%. Mean age of patients was 27.53±4.83, which is in accordance with the study of Dravecka[25] reported 29.33±4.89, 29.2±5.42, 27.6±4.96 in three groups, Elkind-Hirsch K. *et al*[26] reported 28.2±1.1, 27.7±1.3, 32.1±0.7 in three groups, Parveen*et al*[1] reported 26.70 ± 5.20 and 26.60 ± 5.09 in two groups, Jacob R. *et al*[27] reported 27±4, Yousuf R. *et al*[28] reported 27.66 in married and 25.46 years in unmarried patients.

Socioeconomic status: Maximum patients, 36.7%were from upper middle class, 33.3% from lower middle; while 20% and 10% patients were from upper lower and upper class respectively. Kouser*et al*[24] reported 53.33% patients in upper lower class, 24.4% and 22.2% in lower middle and upper middle class respectively; while Parveen*et al*[1] reported 37.5% in lower middle, 32.5% in upper lower and 27.5% in upper middle class respectively.

Marital status: Maximum patients 83.3% were married, which is in consonance with the study of Bangal VB. *etal*[29] reported 80% patients, Alwaeely FA. *et al*[30] reported 90.5% and 87.8% and Parveen*et al*[1] reported 77.5% and 22.5% in two groups respectively.

Age at menarche: Mean age of menarche was 13.2±1.92 which is in conformance with the study of Parveen*et al*[1] reported 13.45±1.09 and 13.30±0.80, Ganie MA. *et al*[31] reported 12.9±1.3 and 13.0±1.2, Balikci A. *et al*[32] reported 12.9±1.0 and 13.0±0.8in two groups.

Mizaj: Most of the patients possessed *Balghami*/phlegmatic (46.7%), followed by *Damwi/*sanguineous(33.3%) *Sawdawi/*melancholic(16.7%) and *safarwi/*bilious (3.3%) temperament. Kouser*et al*[24] reported *balghami, damvi* and *sawdawi* in 71.1%, 20%, and 8.8% of patients respectively, which is consistent with the present study. Moreover, these correlates well with the theories proposed by eminent Unani physicians in pathophysiology of amenorrhoea, as it is caused by abnormal production of *balgham*, which is turn causes *zo'af-i-jigar* resulting in *ihtibas-i-tams.*[11-13]Further, this abnormal *balgham*gets accumulated in sac to form cyst in ovaries.[14,15]

Acne: It was observed in 40% of patients which is in agreement with the study of Gharakhani M. *et al*[33] reported 50%, Ebrahimi F.*et al*[34] reported 39.4%, Astha[35] reported 32%.

Acanthosisnigricans: Majority of the patients, 73.3% had acanthosisnigricans which matched well with the study of Hud*et al*[36] reported 74%, Khanna VN[37] reported 80%. **(Table No-1)**

4.3: Subjective parameters:

Nature of cycle: Before treatment, 100% patients had irregular periods, which become regular in 56.7% and 73.3% patients during 2nd and 3rd cycle of treatment respectively, and in 66.7% patients after treatment; irregular period persist in 6.7% patients in each 2nd and 3rd cycle during treatment and in 20% patients after treatment. Persistent amenorrhoea was observed in 3.3%, 16.7%, and 6.7% patients during 1st, 2nd and 3rd cycle of treatment respectively, and in 10% patients after treatment. Withdrawal bleeding was noted in 63.3%, 20% and 13.3% patients during 1st, 2nd and 3rd cycle of treatment respectively, while 33.3% patients had no bleeding during treatment. Regularity of menstrual bleeding is consistent with the study of Qayyum B. *et al*[38] reported 73% patients had regular cycles and 26% had persistent irregular cycles. (**Table No-2a)**

Duration of cycle: Mean±SD duration of cycle before treatment, after 1st, 2nd and 3rd cycle during treatment and after treatment was 49.17±32.71, 90.17±30.82, 64.45±47.14, 55.43±50.14, and 45.07±43.62 ($p<0.001$) respectively. Duration of cycle was significantly increased in 1st cycle of treatment, and then decreases in subsequent cycles during treatment as well as after treatment.

Duration of flow: Mean±SD of duration of flow before treatment, after 1st, 2nd and 3rd cycle during treatment and after treatment was 4.37±1.54, 2.79±2.53, 4.52±2.00, 4.11±1.45 and 4.73±2.51 respectively. Duration of flow was significantly decreased in 1st cycle of treatment ($p=0.007$), and then remain same in subsequent cycles during treatment as well as after treatment.

Amount of flow: Mean±SD of amount of flow before treatment, after 1st, 2nd and 3rd cycle during treatment and after treatment was 94.03±63.65, 50.53±59.38, 87.90±82.06, 87.40±57.43, 103.97±79.99 respectively. Amount of flow was significantly decreased in 1st cycle of treatment ($p=0.004$), and then remains static in subsequent cycles during treatment as well as after treatment. **(Table No-2b)**

4.4: Objective parameters:

PCOD: On ultrasonography of pelvis, 100% patients had PCOD at base line which persist in 76.66% patients after treatment with a percentage change of 23.34%; while, 20% patients had no PCOD after treatment. **(Table No-3a)**

BMI: Mean±SD of BMI before and after treatment was 29.71±3.87, and 28.89±3.75, respectively with $P<0.001$. Highly significant change in BMI was observed during the study. These findings are compatible with the study of Awalekar J.*et al* [39] reported reduction from 29.58±3.34 to 27.04±3.33 in 3 months, Nemati M. *et al*[40] reported reduction from 29.53±2.75 to 28.34±2.5 in 3 months, Nazari T. *et al*[41] reported reduction from 27.5±4.4 to 26.6±4.1 in 6 months. Israni Da *et al*[42] reported reduction from 26.4±1.08 to 24.85±2.74, 19.16±0.72 to 18.85±0.74 in 3 months treatment in obese and non-obese PCOS patients.

Waist circumference: Mean±SD of waist circumference before and after treatment was 96.10±6.05 and 95.43±6.40 respectively with $P = 0.064+$ considered of suggestive significance, which is in conformance with the study of Tang T. *et al*[43] reported change in from 111.9±13.7 to 108.8±18.2 in 6 months, Nazari T. *et al*[41] reported change from 85.6±13.3 to 84±12.5 in 6 months, This effect is ascribed to antihyperlipidemic, hypoglycemic and insulin sensitizing activities of research drugs.[17,20,21] **(Table No-3b)**

Hirsutism: mFG score ≥ 8 was reported in 30% patients before treatment which persist in same number of patients even after treatment**.** Mean±SD of mFG score of hirsutism, before and after treatment was 5.93±3.42 and 6.03±3.43 respectively. ($P>0.05$) No significant change in mFG score was observed during the trial probably due to

short duration of intervention as minimum 6 months of treatment is required for hirsutism to disappear.[3] **(Table No-3c)**

Sr. LH/FSH ratio: Before treatment, 10% patients had LH/FSH ratio ≤1 which improved in 23.3% patients after treatment with a percentage change of 13%; 60% patients had LH/FSH ratio between 1-2 which lowers in 46.6% patients after treatment with a percentage change of -13%, while 30% patients had LH/FSH ratio >2which persist in 26.6% patients after treatment with a percentage change of 3.4%, Mean±SD of LH/FSH ratio before and after treatment was 1.73±0.67, and 1.72±0.95 respectively with P= 0.833. No significant difference in LH/FSH ratio was observed during the study. **(Table No-3d)**

Ovarian volume: Mean±SD of right ovarian volume before and after treatment was 11.85±4.13 and 10.80±3.77 with P=0.186 (NS). Mean±SD of left ovarian volume before and after treatment was 12.79±4.39 and 10.66±4.47 respectively with P=0.030*, considered moderately significant. Mean ovarian volume before and after treatment was 12.32±4.26 and 10.73±4.12 with P=0.07 (NS). **(Table No-3e)**

4.5: Safety profile: Research drugs was proved to be safe as safety parameters were within normal limits except alkaline phosphatase in which significant change (P=0.016) was observed during the study period and no serious adverse event was reported during the trial.

4.6: Outcome measures:

Primary outcome measure: Withdrawal bleeding was achieved in 63.33% patients. Kouser*et al*[24] reported 62%, Parveen*et al*[1] reported75.0% and 50.0% in two groups, Mokaberinejad R. *et al*[5] reported 68.3%, Yavari M. *et al*[44] reported 72%, Yavari M. *et al*[45]reported 85%. The result of present study matched with the above studies.

Secondary outcome measure: Menstrual regulation was achieved in 73.33% patients. Tariq N. *et al*[46]reported 80% (in 6 months), Athar KSM. *et al*[47] reported 66.7%, Nazari T.*et al*[41] reported 67%, Draveckа*et al*[25] reported 77.8%, 80%, 90% improvement in menstrual cycle in three groups in 6 months. The result of present study is consistent with most of the above studies. **(Table No-4)**

4.7: Strength of the study: The present study is first of its kind where the cause of secondary amenorrhoea was specified and assessment of withdrawal bleeding and menstrual regulation was determined using *Muqil, Murmakki, Abhal* in women with PCOD.

4.8: Limitation of the study: Small number of participants, short duration of treatment, short period of follow up, using fixed dose of research drugs, Serum Insulin, SHBG, Serum DHEA and total testosterone was not done during the study.

4.9: Future Recommendation: Future trial is directed with use of prescribed dosage of research drugs on large number of participants for longer duration with long term follow up for better therapeutic outcome.Further, research is recommended to compare the therapeutic effect of research drugs either with hormonal treatments or life style modification on large sample size atleast for six months.

V. Conclusion

The present study showed that, the oral administration of *Muqil, Murmakki, Abhal*induced withdrawal bleeding in maximum patients (63.33%) of PCOD associated secondary amenorrhoea in first treatment cycle and menstrual regulation (73.33%) in subsequent cycles of treatment.Significant reduction in BMI and waist circumference probably may result in withdrawal bleeding and menstrual regulation which in turn improves the PCOD in 20% patients. This change may also be credited to *mufattih-i-sudad*(de-obstruent),*mulattif-i-khun* (anti-thrombotic)*muharrik,* (stimulant),*qawimudirr-i-hayd* (strong emmenogogue)and *muqawwi-i-jigar*(liver tonic) properties of research drugs *(Muqil, Murmakki, Abhal).* Moreover, research drugs contain steroids and flavonoids, *Mur* contains phytosterol, saponins, terpenoids, lignans, phenolic compounds etc while, *Abhal*contains glycosoids and alkaloids as well, which exert hormone like action in the body and probably may help in withdrawal bleeding and menstrual regulation. Hence, it can be inferred that research drugs may be an effective therapeutic option in patients with PCOD associated secondary amenorrhoea as it has significant effect in inducing withdrawal bleeding and menstrual cycle regulation which in turn improves PCOD. Hence, it can be used as an alternative in its management.

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VII. Conflict of interest

Authors declared that there is no conflict of interest.

References

[1]. Parveen R, Shameem I. Effect of wet cupping in the management of secondary amenorrhoea. STM Journal; A Journal of Unani, Siddha, Homeopathy 2014; 1(1):12-19.
[2]. Beiber EJ, Sanfillip JS, Horowitz IR. Philadelphia. Clinical Gynaecology. Churchill Livingstone Elsevier; 2006: 815-29.
[3]. Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningum FG. Williams Gynaecology. 1st ed. China: McGraw Hill companies; 2008:105-33,365-80,383-99.
[4]. Current evaluation of amenorrhoea. The Practice Committee of the American Society for Reproductive Medicine. WHO Guidelines 2006: Bermingham, Alama; 86(4): S148-55.
[5]. Mokaberinejad R, Zafarghandi N, Bioos S, Dabaghian FH, Naseri M, Kamalinejad M. *Menthalongifolia*syrup in secondary amenorrhoea: A double-blind, placebo-controlled, randomized trials. DARU journal of Pharmaceutical Sciences 2012; 20(97): 1-8.
[6]. Long-term consequences of Polycystic ovary syndrome. Green Top Guidelines No.33. Royal College of Obstetricians and Gynaecologists; 2014 Nov: 1-15.
[7]. Conway G. *et al*. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. European Journal of Endocrinology 2014; 171:1-29.
[8]. Alnakash AH, Al-Tae'e NK. Polycystic ovarian syndrome: the correlation between the LH/FSH ratio and disease manifestations. Middle East Fertility Society Journal 2007; 12 (1):35-40.
[9]. Farshchi H, Rane, Love, Kennedy RL. Diet and nutrition in polycystic ovary syndrome (PCOS): Pointers for Nutritional Management. Journal of Obstetrics and Gynaecology 2007 Nov; 27(8): 762 -73.
[10]. Kort DH, Lobo RA. Preliminary evidence that cinnamon improves menstrual cyclicity in women with polycystic ovary syndrome: a randomized controlled trial. American Journal of Obstetrics &Gynaecology 2014 Nov; 487: e1-6.
[11]. Razi ABZ. Al-HawiFilTib. Vol IX. New Delhi: CCRUM; 2001: 151-68.
[12]. Sina I. Al-QannonFilTib (Urdu translation by Kantoori GH). Vol III. New Delhi: IdaraeKitabulShifa; 2003:1095-98.
[13]. Khan A. Al-Akseer (Urdu translation by Kabeeruddin). Vol II. New Delhi: Ejaz publishing house; 2003:1356-64.
[14]. Firdose KF, Shameem I. An approach to the management of poly cystic ovarian disease in Unani system of medicine: A review. International Journal of Applied Research 2016 May; 2(6):585-90.
[15]. Kermani BDNI. KulliyateNafisi (Urdu translation by Kabeeruddin) Vol I. New Delhi: IdaraeKitabulShifa;YNM: 269-70.
[16]. Arentz S, Abboth JA, Smith CA, Bensoussan A. Herbal medicine for the management of polycystic ovary syndrome (PCOS) and associated oligo/amenorrhoea and hyperandrogenism; a review of the laboratory evidence for effects with corroborative clinical findings. BMC Complementary and Alternative Medicine. The official Journal of the International Society for Complementary Medicine Research (ISCMR) 2014; 14(511):1-19.
[17]. Ghani N. KhazainulAdvia. New Delhi: IdaraeKitabulShifa; 2010:202-3, 206-7, 226,293.
[18]. Anonymous. The Wealth of India. Vol. II. New Delhi: CSIR; 2003:162-63.
[19]. Anonymous. The Wealth of India. Vol. IV. New Delhi: CSIR; 2003: 7.
[20]. Ramesh B et al. Effect of *Commiphoramukul* gum resin on hepatic and renal marker enzymes, lipid peroxidation and antioxidants status in pancreas and heart in fructose fed insulin resistant rats. Beni-Suef University Journal of Basic and Applied Sciences 2015; 4:269-78.
[21]. Helal EGE, Mahmoud A, El-Badawy EE, Kahwash AA. Effect of *Commiphoramyrrha* extract on some physiological parameters and histological changes in diabetic albino rats. The Egyptian Journal of Hospital Medicine 2005 Sep; 20:148–62.
[22]. Elmastas M, Gulcin I, Beydemir S, Kufrevioglu OI, Aboul-Enein HY. A Study on the *in vitro* Antioxidant Activity of Juniper (*Juniperuscommunis* L.) Fruit Extracts. Analytical Letters 2006 Sep; 39: 47- 65.
[23]. Dubey D, Prashant K, Jain SK. *in-vitro* antioxidant activity of the ethyl acetate extract of gum guggul (*Commiphoramukul*) Biological Forum-An International Journal 2009; 1(1):32-35.
[24]. Firdose KF, Begum W, Shameem I. Clinical evaluation of Qillate tams & its management with Unani formulation. International Research Journal of Medical sciences 2013 Dec; 1(11):1-8.
[25]. Dravecka I, Figurova J, Javorsky M, Petrikova, M, Vaľkova, Lazurova M. The Effect of Alfacalcidiol and Metformin on Phenotype Manifestations in Women with Polycystic Ovary Syndrome- a Preliminary Study. Physiol. Res 2016 March; 65: 815-22.
[26]. Elkind-Hirsch K, Marrioneaux O, Bhushan M, Vernor D, Bhushan R. Comparison of Single and Combined Treatment with Exenatide and Metformin on Menstrual Cyclicity in Overweight Women with Polycystic Ovary Syndrome. Journal of Clinical Endocrinology & Metabolism 2008 July; 93(7):2670-78.
[27]. Jacob R, Jude ALC, Chandrasekhar R, Sasika K. Prevalence of Acne among women with Poly Cystic Ovarian Syndrome –a clinical study Scrutiny. International Research Journal of Health and Medical Science 2014; 1(1):7-13.
[28]. Yousouf R, Khan M, Kounsar Z, Ahangar S, Lone WA.Polycystic Ovarian Syndrome: Clinical Correlation with Biochemical Status. Surgical Science 2012 April; 3:245-48.
[29]. Bangal VB, Pushpanjali S, Kanika G, Denita F, Shravani C. Clinical Profile and Outcome of PCOS in Rural Population. Scholars Journal of Applied Medical Sciences (SJAMS) 2014; 2(4E):1465-68.
[30]. Alwaeely FA, Ajlaan SK, Al-assadi AF, Nsaif EM. The prevalence of metabolic syndrome in patients with polycystic ovary syndrome. Thi-Qar Medical Journal (TQMJ) 2011; 5(3):94-102.
[31]. Ganie MA, Khurana ML, Eunice M, Gulati M, Dwivedi SN. Ammini. AC. Comparison of Efficacy of Spironolactone in the Management of Polycystic Ovary Syndrome: An Open-Labeled Study. Journal of Clinical Endocrinology & Metabolism 2004 July; 89(6):2756–62.
[32]. Balikci A. *et al.*Depression, Anxiety, and Anger in Patients with Polycystic Ovary Syndrome. Archives of Neuropsychiatry 2013 March; 51:328-33.
[33]. Gharakhani M, Neghab N, Farimani M. Is Reducing Ovarian Volume in Polycystic Ovarian Syndrome Patients after Administration of Metformin Associated with Improving Cardiovascular Risk Factors. International Journal of Fertility and Sterility 2011 Jul-Sep; 5(2):90-95.
[34]. Ebrahimi F, Enjezab B. Quality of life, general health status and related factors in women of polycystic ovary syndrome in Yazd (IRAN). International Journal of Medical Research & Health Sciences 2016; 5(7S):91-97.
[35]. Dudhat A. Laparoscopic Ovarian Drilling and its Outcome. International Journal of Collaborative Research on Internal Medicine & Public Health 2012; 4(12):2075-83.
[36]. Hud JA, Cohen JB, Wagner JM. Prevalence and significance of Acanthosisnigricans in an adult obese population. Arch Dermatol 1992; 128:941-44.

[37]. Khanna VN. Acanthosisnigricans in type 2 diabetes mellitus patients and its relation with obese women with PCOS and body mass at a tertiary level hospital in central India. International Journal of Recent Scientific Research 2015 July; 6(7):4923-26.
[38]. Qayyum B, Chaudhry SM, Sadaf J. Management of Anovulatory Infertility (Polycystic Ovary Syndrome) with Clomiphene alone and in combination with Metformin. Int. Journal of Surgery Pakistan 2010 Jul-Sep; 15 (3): 135-38.
[39]. Awalekar J, Awalekar C, Vidya M. Jadhav, Chivate CG, Patwardhan MH. Endocrinology effect of metformin in patients of Polycystic Ovarian Disease, a Comparative & Observational Study. SSRG International Journal of Medical Science (SSRG-IJMS) 2015 Sep: 2(9):1-4.
[40]. Nemati M, Nemati S, Taheri A, Heidari B. The Metformin-Induced Changes on BMI, TSH, and thyroid hormones profile of patients with Polycystic Ovarian Syndrome. Reproductive System Sex Disorder 2016 Sep: 5(3):1-7.
[41]. Nazari T, Bayat R, Hamedi M. Metformin Therapy in Girls with Polycystic Ovary Syndrome: A Self-Controlled Clinical Trial. Arch Iranian Med 2007 April; 10(2): 176-81.
[42]. Israni Da, Mehta TY, Shah SR, GoyalRK.Effect of metformin therapy in female visiting dermatologist for Acne vulgaris having endocrine and sonographic characteristics of polycystic ovary syndrome. Asian Journal of Pharmaceutical and Clinical Research 2013 Feb; 6(2):76-82.
[43]. Tang T, Glanville J, Hayden CJ, White D, Barth JH, Balen AH. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. Human Reproduction 2005 Sep; 21(1):80-89.
[44]. Yavari M, RouholaminS,TansazM,Esmaeili S. Herbal treatment of oligomenorrhoea with Sesame indicum L: A randomized controlled trial. GMJ 2016 Aug; 5(3):114-21.
[45]. Yavari M, Rouholamin S, Tansaz M, Bioos S, Esmaeili S. Sesame a Treatment of Menstrual Bleeding Cessation in Iranian Traditional Medicine: Results from a Pilot Study. Shiraz E-Med J. 2014 July; 15(3): 21893.
[46]. Tariq N, Ayub R, Alam AY, Rahim F, Raees SR. Clinical diagnosis of polycystic ovarian syndrome and response to metformin therapy. Journal of the College of Physicians and Surgeons- Pakistan 2007 June.
[47]. 47.Khan S,Shameem I,Sahibole S, Siddiqui A. Efficacy of Unani formulation in infertility among obese women: A clinical study. International Journal of Medical and Health Research 2017 April; 3(4):125-33.

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