International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 03 Issue 04 April 2018, ISSN No. - 2455-8737
Available online at - www.ijirms.in

Open Access Journal | Research Article | DOI: 10.23958/ijirms/vol03-i04/06

Efficacy of *Azadirachta indica* and *Zingiber officinale* on Hirsutism in Polycystic Ovarian Disease: A Randomized Controlled Trial

Dr. Farzana Anjum[1], Dr. Ismath Shameem[*2], Prof. Umraz Mubeen[3]

[1]MS (Ilmul Qabalat wa Amraze Niswan-OBG), National Institute of Unani Medicine, RGUHS, Bengaluru, 560091, India
[2]Lecturer, Department of Ilmul Qabalat wa Amraze Niswan (OBG), National Institute of Unani Medicine, RGUHS, Bengaluru, 560091, India
[3]Professor, Department of Qabalat wa Amraze Niswan (OBG), Govt Unani Medical College, RGUHS, Bengaluru, 560091, India

Corresponding author:

Dr. Ismath Shameem
Lecturer, OBG Department, NIUM. B'lore
Email: dr.ismaths@gmail.com

Abstract:

Background & objectives: *Hirsutism is defined as excessive terminal hair growth on androgen dependent areas of the body in women, which grows in a typical male distribution pattern. Polycystic ovarian disease (PCOD) is the most common cause of it, in 70-80% of women. Hirsutism is recognized to cause profound distress in affected women. Despite of available conventional treatment modalities, its management is still a challenge for physicians. The present study was conducted to evaluate the efficacy and safety of bark of Azadirachta indica (poste darakht Neem) and Zingiber officinale (Zanjabeel) on hirsutism in polycystic ovarian disease.* ***Methods:*** *A randomized controlled clinical study was carried out at Institute's Hospital, Bengaluru. 40 hirsute women with Modified ferriman gallwey score (mFGS) of >6 associated with polycystic ovarian syndrome were assigned to two groups. In test group, decoction of Neem 24 g and Zanjabeel 4 g was given in 2 divided doses and in control group, standard drug (tablet cyproterone acetate 2 mg & ethinyl estradial 0.035 mg) was administered orally from 5th day of cycle for 21 days/cycle for three consecutive cycles for 3 months. Menstrual cycle pattern, ferriman gallway score, body mass index, hormonal assay, lipid profile, pelvic ultrasonography and safety profile were assessed during the trial. Data was analysed with student t test, chi square test and fisher exact test.* ***Results:*** *Fasting insulin ($p=0.030$), lipid profile ($p<0.001$) were reduces significantly in test as compared to control group. Modified ferriman gallwey score ($p=0.950$), body mass index ($p=0.235$), free testosterone (($p=0.185$), and luteinizing hormone ($p=0.203$), reduced in test group similar to control group. Significant improvement of menstrual cycle was reported in control group ($p=0.039$) after treatment. Follicle stimulating hormone remained unchanged in both groups.* ***Interpretation and conclusion:*** *The test drugs poste darakht Neem and Zanjabeel are as effective as control group to improve Modified ferriman-gallwey score, bio chemical and hormonal changes in hirsutism due to PCOD.*

Keywords: ***Hirsutism, Polycystic ovarian disease, Modified ferryman gallwey score, Fasting insulin, Free testosterone, Neem, Zanjabeel.***

1. Introduction

Hirsutism is defined as excessive terminal hair growth on androgen dependent areas of the body in women, which grows in a typical male distribution pattern.[1,2] It's a relatively common condition affecting about 5-10% of women in reproductive age group.[2,3] Regardless of etiology, hirsutism can be a cause of significant mental trauma, decreased quality of life, and low self esteem, where much importance is given to physical appearance.[1,3] Today, the phenomenon of female hirsutism is the focus of psychological and medical research. It is a perplexing issue having variable clinical presentations ranging from severity of hirsutism to altered menstrual history with changes in body mass index and yet some have a positive family history.[4] The causes of hirsutism are divided as androgenic, non androgenic, and idiopathic. Non androgenic factors are relatively rare, while androgenic causes accounts for more than 80% of patients and includes polycystic ovarian syndrome (PCOS) in approximately 90% of women with hirsutism.[1,5] Even hirsutism in its mildest form, may be considered as presumptive loss of femininity[3,6] and poses a serious cosmetic problem for the women[3] and exemplify

itself as a challenging dilemma for management.[7] A women's history and physical examination are particularly important in evaluating the cause of hirsutism. The vast majority of women with hirsutism have the idiopathic variety and the diagnosis is made by exclusion. Although most causes of hirsutism are benign, the treatment is directed to improve the self esteem of the patients. Weight loss should be encouraged in overweight and obese hirsute women as it reduces insulin resistance and androgen production.[1] The treatment options in conventional medicine include combinations of life style modification, mechanical hair removal and medical therapy.[1,3] which though effective but are associated with side effects and complications. Hence the need for natural holistic pharmacological approach is often required in subjects with mild to moderate hirsutism to suppress the androgen production or its action at hair follicles and simultaneously rectifying the underlying cause. Consequently, Traditional medicines have sustained history of practice and are considered as inspiration for current perspective of medicine. It is also a known fact that strength of any medicine depends on continuous scrutiny of past theories, beliefs and practices, which is necessary to promote the development of evidence based medicine with surety of safety and efficacy.[7]

In classical Unani text, hirsutism is mentioned as a complication of prolonged amenorrhoea associated with other masculine features like hoarseness of voice, male body contour, acne etc.[8] *Ibn Sina* and *Ismail Jurjani* explained the basic pathophysiology of hirsutism as variation in normal temperament of women. If amenorrhoea persists for a longer duration, it causes alterations in internal environment of the body and disturbed the equilibrium status of women, leading to growth of excessive hair over the body.[8,9,10] The normal temperament of women gets transformed towards that of men due to prolonged amenorrhoea, which is mainly due to *ehtiraq (*detonation) of normal phlegm (cold and moist) to black bile (hot and dry), which may leads to hirsutism, acanthosis nigricans and acne.[11] It was observed by *Ibn Sina*, *Ismail Jurjani* and *Al-Razi* that development of masculine features is more common in obese women with robust body and prominent blood vessels, as these women have almost similar temperament as that of men.[8,9] *Ibn Sina* states that amenorrhoea is associated with *tulihtibas-i-mani* (chronic anovulation), *farbihi* (obesity),[8]and *uqr* (infertility)[11,12] and such type of women resembles men. Thus, a well established association exists between anovulation, amenorrhoea, obesity, and infertility which correlate with polycystic ovarian disease. Rhazes recommended regular induction of menstruation as one of treatment modality applied for hirsutism in women with PCOD. He has also given treatment option for hirsutism based on correction of temperament and menstrual irregularity by use of emmenagogue single herbs or compound formulations and local application of herbs to reduce severity of hair growth.[13] In Unani system of medicine, several plants and formulations are available for its management possessing the properties of strong emmenagogue, anti thrombotic, deobstruent, hypolipedemic, hypoglycemic, insulin sensitizer and are known to contains phytohormones; among these drugs *Azadirachta indica* (*poste darakht Neem*) and *Zingiber officinale (Zanjabeel*) have been selected for the trial as they are more potent than other drugs[14]

A randomized controlled study was carried in the Dept. of *Ilmul Qabalat wa Amraze Niswan* at National Institute of Unani Medicine, Hospital, Bengaluru. The hypothesis of the study was test drug may be as effective as control drug in hirsutism associated with PCOD. The objective of the study was to evaluate clinically the efficacy and safety of research drugs (*Neem & Zanjabeel)* in hirsutism associated with PCOD. 60 diagnosed cases of hirsutism with PCOD were enrolled & randomly allocated in 2 equal groups. In test group, research drugs was administered orally in decoction form from 5th day of cycle for 21 days/cycle for three consecutive cycles & in control group, standard drug-tablet cyproterone acetate 2 mg & ethinyl estradial 0.035 mg (Tab. Krimson 35) daily once was given for the same duration. The inference was accomplished by appropriate statistical analysis.

2. Materials and Methods:

2.1: Study design: A single blind randomized standard controlled study was carried out in Dept. of *Ilmul Qabalat wa Amraze Niswan*, National Institute of Unani Medicine Hospital, Bengaluru in a duration of one and half year.

2.2: Participants: A total (n=102) patients were evaluated for the study, (n=24) denied to participate and (n=78) were willing to participate. Out of 78, (n=38) were excluded for not meeting the inclusion criteria and (n=40) patients were included in the study & randomly divided in two equal groups, with (n=20) in each group by computer generated simple randomization table.[15]

2.3: Sample size estimation: It was estimated on the basis of previous studies conducted on hirsutism with an assumed mean change in mFGS of 2 in test & 4 in control group as no study of 3 months was accessible for cyproterone acetate; provided 80% to power with a significance level of 5% and dropout rate of 10%, effective sample size of 62 was calculated.[16] However, due to practical feasibility, cost effectiveness and availability of the patients in the hospital, the sample size of 40 was kept and distributed equally in two groups.

2.4: Selection criteria of patients:

Inclusion criteria: Patients in the age group of 14-40 years having hirsutism associated with PCOD along with

menstrual irregularities like oligomenorrhoea or amenorrhoea.

Exclusion criteria: Pregnant and lactating women, patients who had thyroid dysfunction, adrenal & ovarian tumors, systemic illnesses, malignancy and those on hormonal & steroid therapy in last 3 months.

2.5: Study procedure: All patients with hirsutism (mFGS>8) with clinical features of PCOD were evaluated at Gynic OPD of NIUM hospital. Detailed history was elicited from each included patient, and complete physical examination & laboratory investigations like UPT, FBS, thyroid profile, serum total testosterone & pelvic ultra sonography were performed to rule out virilism, pregnancy, diabetes mellitus, thyroid dysfuction, adrenal and ovarian tumors respectively. 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. During the trial, patients were instructed not to take any hormonal pills, not to apply any cosmetics for hair removal and they were asked to maintain the menstrual calendar, diet & physical activity as usual.

2.6: Intervention: In test group, research drugs (*Neem*-24g and *Zanjabeel*-4g)[14] were taken; cleaned, pounded and decoction was prepared in 375 ml of water; *qand siyah* (sugar)-24g was added and administered orally twice daily before meals from 5th day of cycle for 21 days/cycle for three consecutive cycles. In control group, standard drug, Tablet Krimson 35 combination of cyproterone acetate-2 mg with ethinyl eatradiol 0.035mg (Manufactured by Sun Pharmaceutical India Ltd) was given for the same duration.

2.7: Blinding and Compliance: Blinding of patients in either group was maintained as medicine was dispensed in similar pack to one patient at a time. For maintaining patient compliance, drugs were given to patients for 1 month only, informed them to revisit and receive the remainder of the treatment in subsequent follow ups.

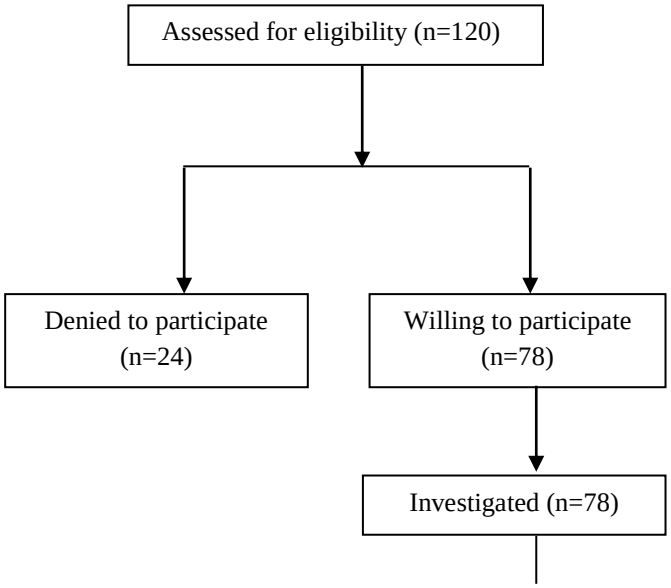
2.8: Follow up: Patients were followed for three consecutive cycles during treatment and one cycle after treatment. During this follow up visit, menstrual cycle pattern, hirsutism score, changes in BMI was assessed and they were also enquired for any adverse drug reaction. Repeat biochemical test, hormonal assay and ultrasound pelvis were carried out after completion of treatment.

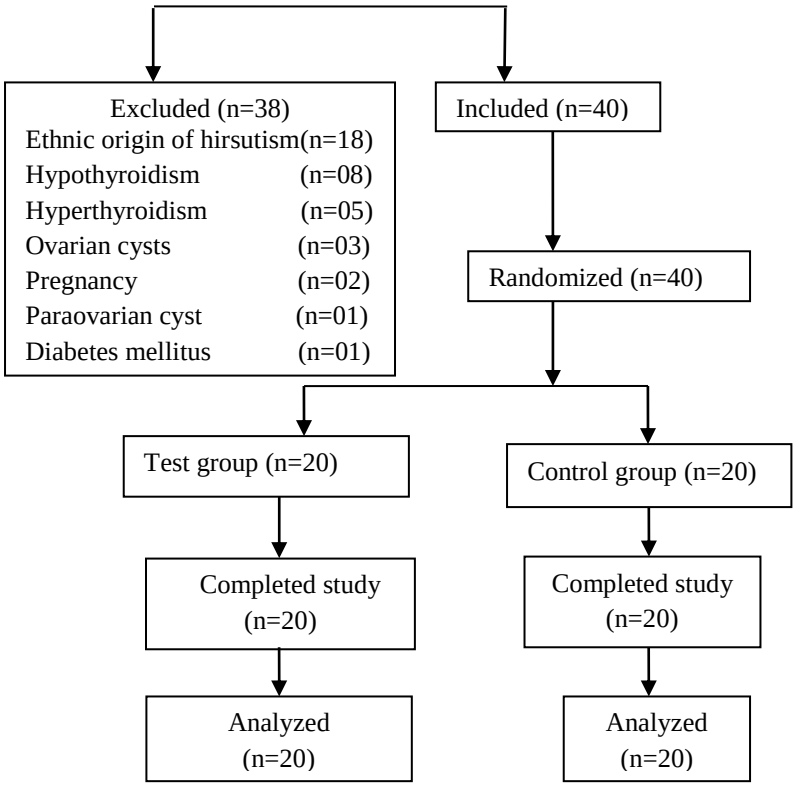
2.9: Assessment of efficacy: Primary outcome measures were changes in mFGS of hirsutism, Serum free testosterone, Serum fasting insulin and secondary outcome measures (improvement in Lipid profile, Serum FSH, Serum LH, USG-Pelvis) were assessed to determine the effectiveness of either therapy.

3. Ethics: Clinical study was started after obtaining ethical clearance from institutional ethical committee and written informed consent was obtained from them.

3.1: Statistics: 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.

+ Suggestive significance (P value: 0.05<P<0.10)
*** Moderately significant (P value: 0.01<P ≤ 0.05)**
**** Strongly significant (P value: P≤0.01**





Trial flow chart

4. Result:

Table 1: Comparison of baseline characteristics in two groups

Baseline characteristics	Test Group (n=20)	Control Group (n=20)	P value
Age (yrs)	25.25±5.24	26.20±6.27	0.606
Marital status • Married • Unmarried	15(75%) 5(25%)	12(60%) 8(40%)	0.311
Age of menarche (yrs)	13.30±0.73	13.15±0.88	0.560
Socioeconomic status • Upper lower • Lower middle • Upper Middle	4(20.0%) 10(50.0%) 6(30.0%)	7(35.0%) 3(15.0%) 10(50.0%)	1.000
Mood disturbances • Present • Absent	17(85%) 3(15%)	16(80%) 4(20%)	0.936
Mizaj • *Balghami* • *Damvi*	6 (30.0%) 14(70.0%)	5(25.0%) 15(75.0%)	0.723
Sr. Total Testosterone(ng/ml)	62.13±12.09	58.37±14.12	0.677

Data were presented as mean ±SD & number (percentage), Student's t-test
Baseline characteristics were statistically similar in both groups

Table 2: Comparison of polycystic ovaries in two groups

Polycystic ovaries	Before Treatment	After Treatment	% change
Test group	20(100%)	6 (30.0%)	70.0%
Control group	20(100%)	4(20.0%)	80.0%

Data were presented as number (percentage), student t test

Table 3: Comparison of BMI in two groups

BMI (kg/m^2)	Before Treatment	After Treatment	P valve
Test group	30.76±4.57	29.58±4.82	<0.001**
Control group	28.61±5.95	27.57±5.55	0.040*
P valve	0.207	0.235	

Data were presented as Mean±SD, Chi-square test/ Fisher Exact test

Table 4: Comparison of menstrual cycle pattern in two groups

Menstrual cycle	BT	During treatment			AT
		1st Cycle	2nd Cycle	3rd Cycle	
DOC (Days)					
Test group	57.00±11.31	35.15±8.31	31.30±5.08	30.74±4.54	30.68±2.38
Control group	60.95±6.20	29.30±2.05	29.00±1.17	28.65±1.18	28.65±3.42
P value	0.179	0.004**	0.056+	0.055+	0.039*
DOF (Days)					
Test group	3.4±1.64	3.9±1.17	3.85±0.93	4.32±0.95	3.79±1.03
Control group	3.75±1.21	4.3±0.66	4.45±0.51	4.25±0.64	4.45±0.69
P value	0.446	0.189	0.016*	0.800	0.023*
AOM(Pads/day)					
Test group	1.50±0.76	1.90±0.45	1.90±0.45	2.11±0.46	2.00±0.00
Control group	2.15±0.67	1.95±0.39	1.90±0.31	2.00±0.00	2.05±0.39
P value	0.007**	0.710	1.000	0.311	0.584

Data were presented as Mean±SD, Chi-square test/ Fisher Exact test,DOC-duration of cycle, DOF- duration of flow, AOF-amount of flow, BT-before treatment, AT-after treatment.

Objective Parameters:

Table 5: Comparison of mFGS of hirsutism in two groups

mFGS	BT	During treatment			AT
		1st Cycle	2nd Cycle	3rd Cycle	
Test group	11.15±4.83	10.9±4.83	9.95±4.65	8.53±4.34	8.53±4.34
Control group	11.05±3.38	10.8±3.07	9.65±3.23	8.45±3.09	8.45±3.09
P value	0.940	0.938	0.814	0.950	0.950

Data were presented as Mean±SD, Chi-square test/ Fisher Exact test, mFGS- modified ferrimangallway score

Table 6: Comparison of objective parameters in two groups

Parameters	Before Treatment	After Treatment	P value
Free testosterone (pg/ml)			
Test group	6.34±4.64	4.11±3.85	0.004**
Control group	4.46±3.26	2.68±2.67	0.040*
P value	0.145	0.185	
Sr. Fasting insulin (µU/ml)			
Test group	17.36±13.08	12.59±8.51	0.021*
Control group	21.34±27.04	19.93±11.53	0.821
P value	0.557	0.030*	
Sr. FSH (mIU/ml)			
Test group	5.59±1.63	5.19±1.83	0.512
Control group	5.55±1.59	4.95±2.11	0.193
P value	0.943	0.709	
Sr. LH (mIU/ml)			
Test group	13.61±10.95	9.90±4.15	0.165
Control group	10.63±5.27	8.07±4.64	0.047*

P value	0.280	0.203	
Sr. Cholesterol (mg/dl)			
Test group	202.25±36.06	188.37±28.02	0.064+
Control group	166.10±24.05	192.60±31.50	<0.001**
P value	0.001**	0.661	-
Sr.Triglycerides (mg/dl)			
Test group	146.35±53.72	134.05±43.09	0.135
Control group	150.60±33.38	168.85±39.61	0.004**
P value	0.765	0.012*	-
HDL (mg/dl)			
Test group	39.95±6.48	44.05±12.91	0.214
Control group	43.20±6.00	42.50±6.35	0.980
P value	0.303	0.634	-

Data were presented as Mean±SD, student t test

Table 7: Comparison of outcome measures in two groups

Outcome Measures	Test group (n=20)	Control group (n=20)	P value
Primary			
• mFGS	20(100.0%)	20(100.0%)	1.000
• Sr. Free testosterone	15(75.0%)	15(75.0%)	1.000
• Sr. fasting insulin	15(75.0%)	8(40.0%)	0.013*
Secondary			
• LIPID profile	15(75.0%)	3(15.0%)	<0/001**
• Sr. FSH	10(50.0%)	8(40.0%)	0.429
• Sr. LH	11(55.0%)	15(75.0%)	0.257
• USG-Pelvis	13(65.0%)	18(90.0%)	0.408

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

5. Discussion:

Baseline characteristics: Mean age of patients was 25.25±45.24 and 26.20±6.27 in test and control groups respectively with P=0.606, which is in accordance with the study of Parveen *et al*[17] reported 26.70 ± 5.20 and 26.60 ± 5.09 in two groups, Rehana *et al*[18] reported 27.53±4.83, Yousuf R. *et al*[19] reported 27.66 in married and 25.46 years in unmarried patients. Even evidence suggest that hirsutism with PCOD is more common in reproductive age group.[20] Mean age of menarche was 13.30±0.73 and 13.15±0.88 in test and control groups respectively, which is in conformance with the study of Rehana *et al*[18] reported 13.2±1.92, Parveen *et al*[17] reported 13.45±1.09 and 13.30±0.80, Ganie MA. *et al*[21] reported 12.9±1.3 and 13.0±1.2. Further, it matched well with the demographic data reported for southern India.[22] Marital status was similar in both the groups with P= 0.31. In test group, 30%, 50% and 20%; while, in control group, 50%, 15%, and 35% patients were from upper middle, lower middle; upper lower class respectively. This shows that, strong relationships exist between the high SES status of patients and hirsutism, as these women tends to have sedentary life style which leads to obesity, insulin resistance and hyperandrogenism.[23] Mood disturbance was observed in 85% patients in test and 80% in control groups respectively. This correlates well with the observations of eminent Unani scholars, who states that women tends to lose their generosity and become hysteric due to prolonged amenorrhoea resulting in hirsutism.[8,24] Most of the patients possessed *Damwi* /sanguineous *mizaj* i,e; 70% and 75% in test and control groups respectively followed by Balghami /phlegmatic i,e; 30% and 25% in test and control group respectively. Moreover, these coincides well with the theories proposed by eminent Unani physicians, who states that when temperament of women shift from normal to abnormal with prolonged amenorrhoea, it results in hirsutism and other masculine features.[25] Mean ± SD of Sr. total testosterone was 62.13±12.09 and58.37±14.12 in test and control group respectively with P=0.677. Raised total testosterone was observed in 25% patients in test and 15% in control groups, which matched well with the study of Ansarin *et al*.[26] Evidence suggest that total testosterone is related with high BMI which probably reflect the insulin effect on theca cells of ovary leading to excess androgen production.[27] **(Table-1)**

USG-Pelvis: All subjects had PCOD at baseline, which persist in 30% and 20% patients in test and control groups respectively after treatment. This action is credited to hypoglycaemic, insulin sensitizing, phytoestrogenic effect of test drugs.[28,29] Further, literature report says that even 5-

10% reduction of initial body weight may regulate the hormonal imbalance and menstrual irregularities by promoting ovulation and improves insulin resistance, thus prevent long term consequences of PCOD.[30] **(Table-2)**

BMI: The Mean±SD of BMI before and after treatment in test group was 30.76±4.57 and 29.58±4.82 respectively with P<0.001**, considered strongly significant and in control group was 28.61±5.95 and 27.57±5.55 respectively with P=0.040,*considered significant. This finding is in consonance with the study of Al-Ruhaily *et al*,[31] Rehana *et al*[18] reported 29.71±3.87, and 28.89±3.75, Awalekar J.*et al*[32] reported reduction from 29.58±3.34 to 27.04±3.33 in 3 months, and Nemati M. *et al*[33]reported reduction from 29.53±2.75 to 28.34±2.5 in 3 months. Further, it is in agreement with literature report which states that 50% patients of PCOD are obese and hirsutism are more common in women with higher BMI.[34] Significant reduction in BMI in test group is attributed to anti-obesity, hypolipedemic and hypoglycemic activities of test drugs, mainly *zanjabeel.*[35] **(Table-3)**

Menstrual cycle: The Mean±SD of duration of cycle before treatment, 1st, 2nd & 3rdcycle of treatment and after treatment were 57.00±11.31, 35.15±8.31, 31.30±5.08, 30.74±4.54, 30.68±2.38 respectively in test group; and 60.95±6.20, 29.30±2.05, 29.00±1.17, 28.65±1.18, 28.65±3.42 respectively in control group. Significant reduction in duration of cycle was observed from baseline to post treatment with in each groups (intra group comparison) and the difference was strongly significant (P=0.039*) in control group than compare to test group (inter group comparison), though remarkable improvement was also noted in test group. The Mean±SD of duration of flow before treatment, 1st, 2nd& 3rdcycle of treatment and after treatment were 3.4±1.64, 3.9±1.17, 3.85±0.93,4.32±0.95, 3.79±1.03 respectively in test group; and 3.75±1.21, 4.3±0.66, 4.45±0.51, 4.25±0.64,4.45±0.69 respectively in control group. Significant improvement in duration of flow was observed from baseline to post treatment with in each groups (intra group comparison) and the difference was strongly significant (P=0.023*) in control group than compared to test group (inter group comparison), though remarkable improvement was also noted in test group. No significant improvement in amount of flow was observed in either group with P=0.584. This action was attributed to medicinal properties of test drugs, which possess *mulattifkhoon* (anti thrombotic), *mufattehsadad* (deobstruent) and *mudirhaiz* (emmenagogue)[10,12,24,25,36] properties which probably may open the blood vessel, liquefy the blood, remove obstruction in blood flow towards the uterus and normalize the uterine function. Hence, *Razi* recommended menstrual regulation as the basic treatment option in patients with hirsutism.[13] **(Table-4)**

mFGS of hirsutism: No significant improvement in hirsutism score was noted in either group, probably due to short duration of intervention as minimum 6 months treatment is required for hirsutism.[3] **(Table-5)**

Free testosterone: The Mean±SD of free testosterone before and after treatment in test group was 6.34±4.64 and 4.11±3.85 respectively with P=0.004**, considered strongly significant and in control group was 4.46±3.26 and 2.68±2.67 respectively with P=0.040*, considered significant; though it was not significant on inter group comparison. Highly significant reduction in free testosterone in test group is attributed to anti-androgenic activity of *neem* due to the presence of active ingredient azadirachtin-A, which may affects the androgen synthesis.[37] *Neem* and *zanjabeel* both possess hypolipedemic effect due to the presence of isoperanoids, which suppress the cholesterol concentration–a substrate for steroid synthesis.[38]

Sr. Fasting insulin: The Mean±SD of Sr. fasting insulin before and after treatment in test group was 17.36±13.08 and 12.59±8.51with P=0.021*,considered significant and in control group was 21.34±27.04 and 19.93±11.53 with P=0.821 (NS); though the difference was significant in control group after treatment with P=0.030*.Significant reduction in Sr. fasting insulin in test group is credited to hypoglycemic effect of *neem* due to the presence of Beta-sitosterol[39] and insulin sensitizing effect of *zanjabeel* due to the presence of active ingredient gingerol which improve the insulin sensitivity.[40]

Sr. FSH: No significant effect on Sr. FSH was noted in either group with P=0.709.

Sr. LH: No significant effect on Sr.LH was noted on intra group comparison (P=0.203), though the difference was significant in control group on inter group comparison with P=0.047 after treatment.

Lipid profile: WRT serum cholesterol, suggestive significant reduction (P=0.064) in test group, and in control group highly significant rise (P<0.001); WRT serum triglycerides, non significant change in test group, while in control group highly significant rise (P=0.004) on intra group comparison and the difference was significant on inter group comparison (0.002*): WRT HDL cholesterol, no significant change was observed during the study. The effect of test drug in increasing the level of HDL cholesterol is significant probably this may be due to reduction in body weight and triglycerides both of which are inversely related to HDL cholesterol in blood. Literature report says that OC pills containing cyproterone acetate and ethinyl estradiol induces an adverse effect on lipid metabolism in women with PCOD resulting in dyslipedemia.[34]

Objective parameters:

The test drugs were safe as safety profile was normal and no adverse effect with test drugs was encountered during the study. **(Table-6)**

Outcome measures: Primary outcome measures were changes in mFGS, free testosterone and fasting insulin; 100% patients achieved changes in mFGS (P=1.000) and 75% patients in free testosterone (P=1.000) in either group; changes in fasting insulin was achieved in 75% in test and 40% in control groups with P=0.013,*considered significant. Secondary outcome measures were improvement in lipid profile, FSH, LH and USG-Pelvis; improvement in lipid profile was achieved in 75% in test and 15% in control groups with P<0.001, considered as highly significant, the difference in FSH, LH and USG-Pelvis was not significant in either group (P>0.05). **(Table-7)**

6. Conclusion

Finally, it can be concluded that the effect of test drugs (*Neem* and *Zanjabeel*) was comparable with that of control drug to reduce hirsutism and free testosterone by inducing menstruation in patients with PCOD due to its anti androgenic, emmenagogue, deobstruent, anti thrombotic properties. Test drugs more efficiently lessened BMI, fasting insulin, cholesterol and triglycerides by hypolipedemic, hypoglycemic and insulin sensitizing effect, thus they improves the insulin resistance and can able to combat PCOD. Hence, it can be inferred that test drugs can be used as a suitable alternative treatment option in patients of hirsutism associated with PCOD. Limitation of the study were small sample size, short treatment duration, short follow up, presence of chronic PCOD in most of the patients. Future trial are recommended on large sample size for longer duration at least for 6 months with long term follow up for better therapeutic outcome.

7. Acknowledgement

The authors are thankful to the Director, National institute of Unani medicine, Bangalore for providing all facilities to complete the research and Dr. KP Suresh, Scientist (Biostatistics), National Institute of Animal Nutrition and Physiology, Bangalore for performing the statistical analysis.

8. Conflict of interest

Authors declared that there is no conflict of interest.

9. References

[1] Hohl A, Ransani MF, Cliveira MD. Hirsutism: Diagnosis and Treatment. Arq Bras Endocrinal Metab 2014; 58(2): 97-107.

[2] Kim JJ, Chae SJ, Choi YM, Hwang SS, Hwang KR, Kim SM *etal*. Assessment of hirsutism among Korean women: results of a randomly selected sample of women seeking pre-employment physical check-up. Human Reproduction 2011; 26(1): 214-20.

[3] Kumar ARV, Thailagavathy VR, Soleti P. Hirsutism: Indian Scenario. The Associations of Physicians of India. www.aplindia.org Chap 66.

[4] Rehman F, Sohail I, Hayat Z, Niazi NA. Etiology of hirsutism. Is there a correlation between menstrual regularity, body mass index and severity of hirsutism. Journal of pakistan association of dermatologist 2010; 20: 4-9.

[5] Faeci, Braunwald, Kasper, Hauser, Longo, Jameson *et al*. Harrison's Principles of Internal Medicine. USA: McGraw-Hill Medical; 2008: 301-04.

[6] Mohammed GFAE. Role of *Cyperus rotundus* oil in decreasing hair growth. J Intercult Ethnopharmacol 2012; 1(2):111-18.

[7] Grant P. Spearmint Herbal Tea has Significant Anti-androgen Effects in Polycystic Ovarian Syndrome-A Randomized Controlled Trial. Phytother. Res. 2010; 24: 186-88.

[8] Sina I. Al-Qannon Fil Tib (Urdu translation by Kantoori GH). Vol III. New Delhi: Idarae Kitabul Shifa; 2003:1095-98.

[9] Jurjani AH. Zakheera Khawarzam Shahi (Urdu translation by Khan HH). New Delhi: Idarae Kitabul Shifa; 2010: 220-25, 590-91, 598-602.

[10] Hamdani KH. Usoole Tibb. 2nd ed. New Delhi: Qaumi Council Barae Farogh Urdu Zuban; 2006: 331-32, 409, 473-75, 485-86.

[11] Razi ABZ. Al-Hawi Fil Tib. Vol IX. New Delhi: CCRUM; 2001: 151-68.

[12] Khan A. Al-Akseer (Urdu trans. by Kabeeruddin). New Delhi: Idarae Kitabul Shifa; 2011: 797-801.

[13] Qumri AMH. GhinaMuna. 1st ed. New Delhi: CCRUM; 2008: 410-13, 435-37.

[14] Ghani N. KhazainulAdvia. New Delhi: Idarae Kitabul Shifa; 2010: 1331-33.

[15] Saghaei M. Random allocation software for parallel group randomized trials. BMC Medical Research Methodology 2004; 4(26):1-6.

[16] Beigi A, Sobhi A, Zarrinkoub F. Finasteride versus cyproterone acetate estrogen regimens in the treatment of hirsutism. International Journal of Gynecology and Obstetrics 2004; 87: 29-33.

[17] 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.

[18] Khatoon R, Shameem I. Effect of *muqil, murrmaki, abhal* in polycystic ovarian disease associated

secondary amenorrhoea. IOSR-JDMS Oct. 2016; 16(10):7-15.

[19] 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.

[20] Noorbala MT, Kefaie P. Prevalence of Hirsutism in Adolescent Girls in Yazd. Central Iran. IRCMJ 2010; 12920:111-17.

[21] Ganie MA, Khurana ML, Eunice M, Gulati M, Dwivedi SN. Ammini. AC. Comparison of Efficacy of Spironolactone in theManagement of Polycystic Ovary Syndrome: An Open-Labeled Study. Journal of Clinical Endocrinology & Metabolism 2004 July; 89(6):2756–62.

[22] Omidvar S, Begum K. Menstrual pattern among unmarried women from South India. Journal of Natural Science, Biology and Medicine 2011; 2(2):174-79.

[23] Merkin SS, Azziz R, Seeman T, Calderon Margalit R, Daviglus M, Kiefe C *et al*. Socioecomonic status and polycystic ovarian syndrome. Journal of Women's Health 2011; 20(3): 413-19.

[24] Ibn Hubal. Kitabul Mukhtarat Fil Tibb. Vol IV. New Delhi: CCRUM; 2005: 31-35.

[25] Majusi ABA. Kamilus Sana (Urdu trans. by Kantoori. GH). New Delhi: Idarae Kitabul Shifa; 2010: 110-12, 533-35.

[26] Ansari H, Aziz-Jalai MH, Rasi A, Arabshahi RS. Clinical Presentation and Etiological Factors of Hirsutism in Premenopausal Iranian Women. Arch Iranian Med 2007; 10(1):7-13.

[27] Franks S. Polycystic Ovarian Syndrome in Adolescent. International Journal of Obesity 2008; 32:1035-41.

[28] Anonymous. The Wealth of India. Vol. I (A). Vol. IX(X-Z) New Delhi: NISCIR; 2004:501-11, 89-104.

[29] Ivan A Ross. Medicinal plants of world. Vol.II. New Jersey: Humana Press; 2001:81-101, 507-43.

[30] Hoeger K, David K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives, and life style modifications on Polycystic Ovarian Syndrome in obese Adolescent women in two randomised placebo controlled clinical trial. J clin endocrinal metab. 2008 Nov; 93(11): 4299-06.

[31] Al-Ruhaily AD, Malabu UH, Sulimani RA. Hirsutism in Saudi females of reproductive age: A hospital based study. Ann Saudi Med 2008 Jan-Feb; 28(1): 28-32.

[32] 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.

[33] 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.

[34] Elter K, Imir G, Durmusoglu F. Clinical endocrine & metabolic effects of metformin added to ethinyl estradiol- cyproterone acetata in non obese women with PCOS: A Randomised Controlled Study. Human Reproduction 2002; 17(7): 1329-37.

[35] Mahmoud RH, Elnour WA. Comparative evaluation of efficacy of ginger and orlistat on obesity management, pancreate lipase and liver peroxisomal catalase enzyme in male albino rats. European review for medicinal and pharmacological sciences 2013; 17:75-93.

[36] Ibn Zuhar. Kitabul Taiseer Fil Mudawat wa Tadbeer. 1st ed. New Delhi: CCRUM; 1986: 185.

[37] Aladakatti RN, Sukesh B, Jadaramkunti UC, Hiremath MB. Aspects of the antiandrogenic property of Azadirachtin-A from *Azadirachta indica* leaves in male albino rats; effect on the biochemical and cauda epididimal sperm parameters. Recent Research in Science and Technology 2011; 3(2): 34-46.

[38] Craig WJ. Health promoting properties of the common herbs. Am J Clin Nutr 1999; 70(suppl): 491S-9S.

[39] Banaszewska B, Pawelczyk L, Spaczynski RZ, Dziura J, Duleba AJ. Effect of Simvastatin and Oral Contraceptive Agents on Polycystic Ovarian Syndrome: Prospective Randomised Crossover Trial. Journal of clinical endocrinology & metabolism 2007; 92(2) 456-61.

[40] Li Y, Tran VH, Duke CC, Roufogalis BD. Preventive and protective properties of *Zingiber officinale* in Diabeted Mellitus, its complication and associated lipid and other metabolic disorders: A review. Evidence Based Complimentary and Alterrnative Medicine 2012; 1-10.

