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CLINICAL STUDY TO VALIDATE THE THE EFFICACY AND SAFETY OF UNANI FORMULATION IN MENOPAUSE

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ABSTRACT

"*Sinne ya's*" (Menopause) which means period of *Zamane naumaidee* (hopeless period). According to unani physician the whole human body is divided in to four age groups, which are consider to carry their particular *mizaj*. The age group of 35-60 years is known as *sinne kahulat* in which *mizaj* becomes *barid* (cold) and *yabis* (dry). It is believed that, *Ehtebaz haiz* (stoppage of menses) in women of this age occurs naturally due to change of *mizaj*. In Modern system of medicine, Menopause, a natural step in the aging process, represents the end of menstruation after the last menstrual period in the previous 12 months. The World Health Organization has defined the menopause as the permanent cessation of menstruation resulting from loss of ovarian follicular activity (World Health Organization, 1996). As the ovaries becomes less functional they produce less of these hormones and body responds accordingly. Primary menopausal symptoms are considered to be the vasomotor symptoms, referring to hot flushes and night sweats. The vasomotor symptoms may also be associated with sleep and mood disturbances, as well as decreased cognitive function. Other menopausal symptoms are urogenital atrophy, urinary tract infections and incontinence, somatic symptoms, sexual dysfunction and decreased libido, and loss of skin elasticity. The treatment strategy of menopausal syndrome has been to replace the deficient oestrogen. This strategy of hormone replacement has got alarming physical hazards. Phytoestrogen are naturally occurring plant compounds that are similar in some ways to estradiol, the most potent

naturally occurring estrogen. The unani formulation in the study was effective and safe than placebo for ameliorating somatic, psychological and urogenital symptoms at post intervention the thereby improving HRQoL.

INTRODUCTION

Unani medicine, as is well known, based on the Hippocratic humoral theory. This theory supposes the presence of four humuors in the body viz: blood, phlegm, yellow bile and black bile. The *mizaj* of individuals are expressed by word *damawi* (sanguine), *balghami* (phlegmatic), *safrawi* (choleric) and *saudawi* (melancholic). According to the dominancy of the humour every person is supposed to have a unique humoral constitution which represents his healthy state and any change in this state causes illness of the said person. The severity of the disease depends directly upon the change in equilibrium from *mizaj*.[1]

In Unani literature, **"*Sinne ya's*" (Menopause) which means period of *Zamane naumaidee* (hopeless period).** According to unani physician the whole human body is divided in to four age groups, which are consider to carry their particular *mizaj*. The age group of 35-60 years is known as sinne kahulat in which *mizaj* becomes *barid* (cold) and *yabis* (dry). In this age, production of *ratubate unsirya* is decreased, so much that it is insufficient to maintain *harartae unsirya* and all the *quwa* (power) starts deteriorating.[2] It is believed that, *Ehtebaz haiz* (stoppage of menses) in women of this age occurs naturally due to change of *mizaj*. It was the Hippocrate (460-377BC) who firstly postulated the concept of disease is due to the imbalance of humors and hence emphasized on natural knowledge and hence freed medicine from the realm of superstition and magic, and gave it the status of science.[3,4,5,6] He mentioned in his book *Tabiatul insaan*(Human Nature) *Khilat-e-Sauda*, (Black Humor) is *barid* and *yabis* and elderly person are *barid* and *yabis* by temperament so it is dominant in this age group.

In Modern system of medicine, Menopause, a natural step in the aging process, represents the end of menstruation after the last menstrual period in the previous 12 months. The World Health Organization has defined the menopause as the permanent cessation of menstruation resulting from loss of ovarian follicular activity (World Health Organization, 1996). The perimenopause commences when the first feature of approaching menopause begins until at least 1 year after final menstrual period (FMP). The ovary is the only endocrine gland that stops functioning before the final stages of life. The symptoms of menopause are caused by

changes in estrogen and progesterone levels. As the ovaries becomes less functional they produce less of these hormones and body responds accordingly.

The transition from active reproductive life to inactive postmenopause is not always a smooth one. Due to aging, hormonal reversal and concomitant reluctance to adopt the new norms of postmenopausal life, women invariably are stressed and react in the form of somatic, vasomotor, and psychological disturbances, that constitute menopausal syndrome. Variety of problems occurs at or after menopause which are due to oestrogen deprived or relatively oestrogen deficient status of these women. The treatment strategy of menopausal syndrome has been to replace the deficient oestrogen. This strategy of hormone replacement has got alarming physical hazards. It is associated with increased risk of endometrial hyperplasia and carcinoma breast, ovarian cancer, stroke, gall stones and venous thromboembolism.Although HRT prevents osteoporosis and fracture at 75 years but causes carcinoma at 55 years.

Therefore patients as well as physicians are increasingly interested to explore new options for the management of menopausal symptoms such as complementary therapies using natural products with good effectiveness and fewer side effects.[7]

Phytoestrogen are naturally occurring plant compounds that are similar in some ways to estradiol, the most potent naturally occurring estrogen.[8] Isoflavones are phyto-estrogens similar to women's estrogens and are bound to cellular estrogen receptors in various organs, thus phytoestrogens affinity is weak compared to human's estrogens. Recent studies have shown that cells have two types estrogen receptors α and β. Human estrogens have more affinity to α-receptors, whereas, isoflavones have high affinity to β-receptors. β-receptors exist in brain, bone, bladder and vascular epithelium, being important in the function of non-steroid estrogens.[9]

The primary objective was to compare the effectiveness and safety of Unani formulation with placebo in alleviating somatic, psychological and urogenital symptoms using menopausal rating scale (MRS). The patients were assessed for various symptoms like hot flushes and night sweats depression, anxiety, loss of concentration and memory, insomnia, urinary symptoms headache, irritability and by various scales of measurement at time intervals of 0 day, 15 days, 1 month till 3 months, with a follow up observations. Both the test and control groups were analyzed and compared statistically by using appropriate tests, the claims of Unani physicians for Unani formulation will be validated scientifically, where in we may get a safe cost effective and efficacious drug for the management of menopausal

syndrome from the natural source, the availability of the ingredients will make it a new natural–human relationship for the benefit of humans with a rational base.

METHODOLOGY

Research question, hypothesis and objective of the study

The research question was whether unani formulation was effective and safe in relieving somatic, psychological and urogenital symptoms of menopausal syndrome using the validated Health-Related of Quality of Life (HRQoL) questionnaire, Menopause Rating Scale (MRS).

Study site The proposed study was conducted in OPD & IPD of the department of Ilmul Qabalat wa Amraz-e-Niswan, A & U Tibbia College & Hospital, Karol Bagh, New Delhi - 05.

Study design: Prospective, single center, single-blind, simple randomized, placebo controlled parallel design study.

Study Population

Women within age group of 40-55yrs.

Study Duration

One Year.

Duration of Protocol Therapy:

3 Months.

Sample Size:

Total patients-80=Test group-40 patients.

Control group-40 patients.

Sampling Technique.

Through randomization and blinding

The patients were randomly allocated in a l:1 ratio by computer generated random list into test and control group The participants were blinded by masking and matching the test and control group.

Participant's selection

A total of 80 patients (excluding 5% dropout) presenting with menopausal syndromes for at least two months who fulfilled the inclusion criteria were recruited.

Method of Collection of Data-

Procedure: The pre randomization screening visit included a history, physical exam, gynaecological exam, menopausal rating scale questionnaire and investigations. The socioeconomic history included monthly income, education and occupation, assessed by Kuppuswamy's Socioeconomic Scale.

Criteria For Selection of Patients

Patient of menopausal syndrome clinically assessed will be included in the study after obtaining their voluntary consent.

Inclusion criteria

Women within age group of 40-55yrs, with chief complaints of menstrual irregularities, hot flushes, cold sweats, sleep disturbances, palpitation, arthralgia, fatigue, anxiety, depression, urinary and sexual problems and willing to participate in the study.

Exclusion criteria

Patients with systemic illness, with past history of taken HRT within two months.Patients with any kind of malignancies, tumors or any pelvic pathology, pregnant and lactating women. Women with undiagnosed vaginal bleeding, history of surgical menopause and Patients not willing to report for follow up.

Investigation

The following examinations will be performed for the exclusion of any concomitant acute and chronic diseases.

Complete Blood Count, Blood Sugar Random, KFT, LFT, Thyroid profile, Serum estrogen, LH/FSH, Pelvic scan.

These routine examinations will be done before the commencement of protocol therapy to rule out systemic illness, assessment will be done by history taking, clinical examination & investigation if needed.

Informed Consent

Volunteers who fulfill the above mentioned inclusion and exclusion criteria will be given the Patient Information Sheet (in the language she was familiar with). If they agree to participate in the study they will be asked to sign the Informed Consent Form.

Intervention

The trial drug, unani formulation has been selected from the Unani literature. This herbs was purchased from the Rehan Matab.

COMPOSITION OF THE TEST DRUG

S.No	Name of Drug	Scientific Name	Quantity
1	Afteemoon	*Cuscuta reflexa*	3 grams
2	Soya	*Anethum graveolens*	5 grams
3	Bisfayij	*Polypodium vulgare*	3 grams
4	Satavar	*Asparagus recemosus*	5 grams
5	Zaravand mudharaj	*Aristolochia rotunda*	3 grams
6	Asgandh	*Withania somnifera*	5 grams
7	Qand safaid	*Sugar*	Q.S

The above mentioned drugs were authenticated pharmacognostically by the Scientists of NISCAIR, New Delhi.

For control group-: Placebo:-orally-wheat flour with sugar in powder form.

Method of Preparation

For test group

After cleaning, the trial drug after was pounded, sieved and mixed well to make fine powder. Unani formulation powder and placebo (wheat flour with sugar in powder form) 6 gm was administered orally in two divided doses for 3 month.

Criteria For The Assessment of Efficacy

Assessment of efficacy done by using the following parameters.

Subjective parameters

- Patients with history of menstrual irregularities, hot flushes, cold sweats, sleep disturbances, palpitation, arthralgia, fatigue, anxiety, depression**,** urinary and sexual problems.

Objective parameters

- Assessment by Menopausal Rating Scale (MRS).
- Hot flushes and sweating will be assessed with number of episodes in 24hrs.
- Estrogen levels
- LH/FSH

HRQoL measurement (MRS Questionnaire): Menopause Rating Scale consisted of 11 items assessing menopausal symptoms, divided into three subscales:-

A. **Somatic:** Hot flushes, heart discomfort, sleep problem and muscles and joint problems.
B. **Psychological:** Depression, irritability, anxiety and physical and mental exhaustion.
C. **Urogenital:** Sexual problems, bladder problems and dryness of vagina.

A 5 point rating scale permits the patient to describe the perceived severity of complaints graded from **0-4, (0 = not present), (1= mild), (2=moderate), (3=severe), (4=very severe)** by checking the appropriate box. For the present study the MRS english version was used. The composite score for each of the sub-scales is based on adding up the scores of the items of the respective dimension scores.

Parameters For Assessment of Safety

The safety assessed by monitoring adverse events either volunteered by the patients or elicited by the investigator before treatment after 15 days & after completion of treatment by monitoring the following.

- Clinical assessment at every visit, Adverse drug reaction, Biochemical assessment
- KFT, LFT, TLC, DLC, ESR.

These parameters indicate the renal and hepatotoxicity of the test substances with specificity and systemic toxicity in general.

Withdrawal Criteria

Failure to consume the drug, report for follows up, Any significant adverse drug reaction or adverse event.

Criteria For The Assessment Of Result

Grading of Response in terms of improvement in following parameters.

S.No	**Parameters**	**0 Day**	**30 Day**	**2 Month**	**3Month**
1.	Hot flushes				
2.	Heart discomfort				
3.	Sleep problem				
4.	Depression				
5.	Irritability				
6.	Anxiety				
7.	Physical & mental exaution				
8.	Sexual problem				
9.	Bladder problem				
10.	Dryness of vagina				
11.	Joint & muscular discomfort				

DATA ANALYSTS

Statistical software: The Statistical software Graph pad Instat versini 3.00 for window (Graph Pad Software, Social Statistic, Math portal), and the contingeiry table of more than 2x2, online website (htgrllwww.physic&csbju.edu/cgibinlstats/a) was used for the analysis of the data and Microsoft word have been used to generate graphs, tables etc.

STATISTICAL ANALYSIS

Descriptive analysis was performed by means of the frequencies of the category variables and measurements of the position and dispersion of the continuous variable & Results on continuous measurements were presented on Mean ±SD.(Min-Max) and results on categorical measurements were presented in number (%) for all statistical test, 2 sided P values was used and type 1 error was set as 0.05 & 95% confidence interval. The following assumptions on data are made.

Ethical Issues

Ethical consideration The Institutional Ethical Committee approved the present study both written and oral information about the reasons of the present study were given in local language to women and invited to participate.

DISCUSSION

BASELINE CHARACTERISTICS

1	**Age group**	**Test group**	**Control group**	**Total number and Percentage**
	40-42	1…….1.25%	1……..1.25%	**2……2.5%**
	43-45	4……..…5%	4……5%	**8……...10%**
	46-48	7…….8.75%	10……..12.5%	**17……..21.25%**
	49-51	19……23.75%	12…….15%	**31……38.75%**
	52-55	9……11.25%	13……..16.25%	**22……27.5%**

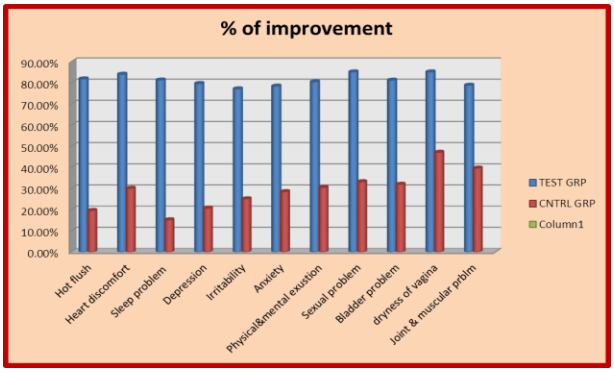
	Total	40……..50%	40….50%	**80…..100%**
	Religion			
	Hindu	6	5	**13.75%**
	Muslim	34	35	**86.25%**
	Othr	0	0	**100%**
	Diet			
	Veg	4	2	**7.5%**
	Non veg	36	38	**92.75%**
	Socio-economic status			
	Lower class	12	9	**26.25%**
	Upper lower class	11	15	**32.5%**
	Upper middle class	17	16	**41.25%**
	Mizaj			
	Harart e rehm	7	6	**13(16.25%)**
	Burudat-e-rehm	30	31	**61(76.25%)**
	Rutubat-e-rehm	1	1	**2(2.5%)**
	Yabusat-e-rehm	2	2	**4(5%)**

The present prospective, single-blind, placebo-controlled, simple randomized study was conducted to assess and compare the efficacy and safety of Unani composition in alleviating somatic, psychological and urogenital symptoms of menopausal transition using the validated Health-Related Quality of Life (HRQoL) questionnaire, Menopause Rating Scale (MRS). Till date, clinical studies, evaluating the efficacy and safety of the Unani composition in reducing menopausal symptoms are deficient.

Therapeutic outcome:

parameter	**Test group (n=40)**	**control group (n=40)**	**Mean diff.of TG&CG**	**P=valve**	**Comparison from base line**			
					TG		CG	
					AC	% chng	AC	%chng
Hot Flushes(0)	2.475+.838	2.675±.693	.200	.3261				
90th day	.45+.5524	2.15+.6223	1.70	.00008	2.025	81.81%	.525	19.6%
Heart discomfort	2.35+.5856	2.65+.7375	.2750	.0681				
90th day	.375+.5401	1.85+.7355	1.475	.000012	1.975	84.0%	.80	30.1%
Sleep problem (0)	2.4+.5495	2.625+.6400	.225	.1378				
90th day	.45+.5038	2,225+6197	1.775	.000010	1.95	81.25%	.40	15.2%
Depression (0)	2.45+.6385	2.65+.6223	.200	.4802				
90th day	.5+.5547	2.1+.7442	1.60	.000009	1.95	79.6%	.55	20.7%
Irritability(0)	2.60+.7403	2.475+.6789	.125	.3478				
90th day	.60±.6325	1.85±.5796	1.250	.000029	2.000	77.1%	.62	25.1%
Anxiety(0)	2.55±.6325	2.625±.6279	0.075	.8596				
90th day	0.55±.597	1.875±.8224	1.325	.000028	2.00	78.4%	.75	28.5%
Physical & mental exaustion(0)	2.425±.6789	2.70±.6485	0.275	.1386				

90th day	.475±.5058	1.875±.8224	1.400	.000010	1.95	80.4%	.825	30.5%
Sexual problem(0)	2.35±.6789	2.625±.7507	.275	.1287				
90th day	0.35±.483	1.75±.7071	1.40	.000009	2.000	85.10%	.875	33.2%
Bladder problem(0)	2.40±.7442	2.575±.7472	.175	0.4557				
90th day	.450±.5524	1.75±.8397	1.30	.00001	1.95	81.2%	.825	32%
Dryness of vagina(0)	2.35±.6718	2.6±.7442	.200	.2108				
90th day	0.35±.483	1.375±.8066	1.025	.000070	2.00	85.1%	1.225	47.1%
Joint & muscular problem(0)	2.600±.7742	2.9±.7779	.300	.1171				
90th day	.55±.6385	1.75±.9541	1.20	.000030	2.05	78.8%	1.15	39.6%



The primary outcome was to compare the efficacy and safety assessment of unani formulation with placebo in ameliorating menopausal transition symptoms thereby improving HRQoL assessed by MRS.

The inter group comparison for MRS total score and somatic, psychological and urogenital subscales score at post intervention was statistically significant (P<0.000l) between the groups. The intra group comparison for MRS total score and somatic, psychological and urogenital subscales score was statistically extremely significant (P<0000l) at each visit compared with baseline in both groups.

The percentage improvement for MRS total score, somatic subscale, psychological subscale and urogenital subscale score in control group was 66%, 67% and 54% respectively compared to baseline.

It was also noted that in test group maximum improvement was noted for the dryness of vagina (85.10%), sexual problems (85.10%), heart discomfort (84.0%), hot flushes (81.81%), bladder problems (81.25%), sleep problem (81.44%), physical and mental exhaustion

(80.4%), depression (79.6%), joint and muscular discomfort (78.8%), anxiety (78.43%), followed by irritability (77.1%).

Each of the 11 specific symptoms of MRS was statistically not significant at baseline (P>0.05). Post intervention, between the group comparison was statistically significant (P<0.05) for hot flushes, heart discomfort, sleep disturbance, depression, physical and mental exhaustion, bladder problem, joint and muscular discomfort symptoms.

In each of the 11 individual symptoms, percentage change was more than 60% in the test group, whereas in the control group it was less than 30% except bladder & dryness of vagina problems (32%) and 47% respectively.

Safety profile

All the biochemical parameters were comparable and statistically not significant when compared from baseline in both groups except SGOT (P=0.02), SGPT (P=0.007), in the control group, and alk.phos. (0.0038) in control group, which was statistically significant but laboratory value was within normal range. This shows that the test drug did not cause any harm to the organs and body fluids.

	Test group		Control group	
Safety parameter	**At-Baseline**	**At-post treatment**	**At-Baseline**	**At-post treatment**
SGOT	27.45±5.698	28.80±4.952	27.47±7.71	30.85±5.30
SGPT	26.65±9.379	28.15±6.9818	25.07±8.17	29.57±6.19
Alk.Phospt.	105.0±33.15	96.55±30.29	96.67±25.85	94.70±26.26
Bl.Urea	27.80±5.179	25.45±6.372	27.47±6.52	25.95±5.29
S.Creatinine	0.85±0.110	0.73±0.226	0.84±0.16	0.75±0.24

CONCLUSION

The primary objective was to compare the effectiveness and safety of unani formulation with placebo in alleviating somatic, psychological and urogenital symptoms using menopausal rating scale (MRS).

The unani formulation was effective and safe than placebo for ameliorating somatic, psychological and urogenital symptoms at post intervention the thereby improving HRQoL. The drugs composing the formulation has long been in use as a Unani drug for different ailments such as *ehtabas-e-haiz* (amenorrhea), *amraz-e-rehm* etc as it has *mudir-e-haiz* (emmenogogue), *mudir-e-baul* (diuretic), *muqawwi-e-bah* (aphrodisiac), *kasir-e-riyah* (carminative), *muqawwi-e-asab* (nervine tonic) properties.

Phytochemically these drug contains steroids, saponins, flavonoids, alkaloids, unsaturated fatty acids, glycosides, vitamins, tannins, resins, nitrate potassium, aspartic acid and glutamic acid.

Overall the test drug was effective probably because of estrogenic, aphrodisiac, CNS activity, anti-inflammatory, anti-oxidant, analgesic, antispasmodic, nervine tonic and diuretic effect.

Scope for Further Study

The present clinical trial to evaluate the Efficacy & Safety of Unani Formulation "Menopause" was in itself, properly planned and executed according to the protocol. Best possible efforts were made to achieve accurate and conclusive results in the study. Nevertheless no research is complete and there is always room for further improvement. The present study, being a time bound programme, the sample size was small (80 patients). Looking at the positive and encouraging results in the present study, it is sincerely felt, that with a larger sample size subjected to certain other sophisticated investigations, more in-depth analysis could be carried out.

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