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Clinical trial of Unani herbomineral cream to evaluate its topical effects on Acne vulgaris

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A controlled, randomized single blind clinical trial was conducted as per GCP guidelines for the duration of 2 months on the human individuals suffering from acne vulgaris. The patients were divided into 2 groups, control group treated topically with only cream base and the test group treated topically with the UHC. The effects of the Unani herbomineral cream (UHC) were scientifically evaluated in human beings in acne vulgaris. The assessment of the severity of acne vulgaris in the control and test groups was made by the Investigators Global Acne Severity Score. The statistical analysis of the results of severity of acne vulgaris in the control and test groups was made for the total duration of treatment. Group comparisons (within and inter group) were made using ANOVA and paired t- test respectively. The effect of only cream base did not show any significant improvement in the acne vulgaris of the patients of control group. On the other hand, the within group and inter group comparisons in the test group showed significant differences at each stage of the treatment. The test drug, UHC has been proved effective in the treatment of acne vulgaris in the test group in comparison to the control group.

Keywords: Unani medicine, Acne vulgaris, Unani herbomineral cream

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Acne vulgaris is a common disease, which affects almost 90% of population sometimes in life. It is self limiting in majority and minor forms heal without scaring[1]. In Unani System of Medicine, Acne vulgaris, called as *Busoor-e-Labaniyah* (eruptions of milk) due to whitish discharge resembling milk is a chronic inflammatory disease of the sebaceous glands and pilosebaceous structures of the skin[2-5]. It occurs most commonly among teenagers[6]. Lesions may begin as early as age 8-10 yrs at *Sebarche*, which in girls may precede menarche by more than a year. Prevalence increases steadily throughout adolescence and then decreases in adulthood[7-8]. According to Unani physicians, the main cause of *Busoor-e-Labaniyah* is the hyperactivity of *Ghudud-e-Dohniya* (sebaceous glands), which results into increased production of oily material, which gets clogged into the openings of these glands ,these glands are then inflamed and get suppurated and filled with pus[2,4,6,9]. The yellow *madah-e-sadeedi* (pus) reaches to the skin due to e*frat-e-hararat* (increased abnormal heat) and does not resolve easily from the pores[2]. In others words, the *mada-e-sadeediyah* originates due to the *bukharat-e-badan*, which are shifted towards skin[3]. The yellow liquid of *busoor-e-labaniyah* is transformed from the *bukharat* of the body, which are accumulated in the skin and their *raqeeq* (light) ingredients get converted into a thick fluid due to the affect of air and these thick materials are not easily resolved and the pores get blocked[10]. There are many causes which lead to the above described pathogenesis, such as disturbances of the blood (impurities), use of hot diets, use of alcohol, indigestion, menstrual disturbances, etc[2,11].

The most common drugs, which are used for topical treatment of acne are Adapalene, Azelaic acid, Benzoyl peroxide, Clindamycin, Erythromycin, Erythromycin plus, Isotretinoin, Meclocycline, and tetracycline[12]. It is recommended that topical retinoid are not used in pregnancy or by women of child bearing age, who are not taking adequate contraceptive precautions. Azelaic acid was associated with itching, stinging, burning and erythema. Benzoyl peroxide increased the proportion of people who had adverse effects, including dryness,

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scaling, burning, tingling, and redness. Isotretinoin was associated with severe erythema, dryness, and soreness and burning. Topical tetracycline was associated with skin discoloration. Tretinoin was associated with erythema, peeling, burning and pruritus[12]. The drugs used orally for the treatment of acne, are Doxycycline, Erythromycin, Lymecyclin, Minocyclin, Oxytetracycline and Tetracycline[12]. Erythromycin, Lymecycline, Minocycline, Oxytetracycline may cause contraceptive failure. Tetracycline may harm bones and teeth and should not be taken by pregnant or breast feeding women[12]. There are strong possibilities that some drugs of natural origin, either from plants or minerals would prove effective and safe. Therefore in the study, a Unani herbomineral cream (UHC) prepared and formulated with the natural drugs was evaluated for its possible usefulness in acne vulgaris. The clinical trial was carried out as a single blind study in which the human individuals were not aware of the nature of the treatment.

Methodology

A controlled, randomized, single-blind clinical trial was conducted as per the GCP guidelines on the individual suffering from the acne vulgaris. The permission of the Institutional Ethics Committee (IEC) was taken prior to the initiation of the clinical trial. The ingredients of the test Unani herbomineral cream formulation (UHC) were taken from the authentic sources. Further, the quality assurance was made on the basis of description given in the classical Unani literature as well as botanical sources. The selected individuals suffering from acne vulgaris were randomly divided into 2 groups, control group (10 individuals) and test group (20 individuals) and the total duration of study on the individual was 60 days. Females between the ages of 15-35 yrs suffering from acne vulgaris were included in the study. The patients suffering from diabetes, hypertension, renal disorders, cardiac diseases, severe psychiatric disorders and other life threatening diseases such as hepatitis, AIDS, etc. were excluded from the study. The pregnant/lactating women were also excluded from the study.

The test drug, UHC was prepared from *Irsa* (root), *Neem* (leaves), *Nagarmotha* (root), *Harsinghar* (stem) extracted in the petroleum ether (60:80) in the Soxhlet'*s* Apparatus. The *Anzroot* was extracted in the alcohol-distilled water (50:50). The aqueous extract of the *sibr* was produced from the authentic source. The essential oils of the *Baboona*, *Khus*, *Murmakki, Kundur, Chameli* and the fixed oils of *Badam* and *Zaitoon* and the fine powder of *Safaida Kashghari* were also procured from the authentic sources (Table 1). The cream base was prepared from stearic acid, cetostearyl alcohol, bees wax (white), liquid paraffin, lanolin and petroleum jelly melted in a steam bath at 75°C. The remaining ingredients were dissolved in the purified water at 75°C. The aqueous solution was added to the oily face with agitation. Excessive agitation was avoided to prevent the air to be entrapped in the cream. The cream base was divided into two parts. One part was kept for the control group and the other part was mixed with drugs of the test formulations (Table 2). The ingredients of the test formulations were added stepwise into the cream base. The fixed oils, powders and the extracts

Table 1—Composition of Unani herbomineral cream used for the study

Drugs	Local name	Forms used	Scientific name	Percentage
Irsa root	*Irisa / Sosun*	Extract	*Iris ensata* Thunb.	1.5%
Neem leaves	*Neem*	Extract	*Azadirachta indica* A.Juss.	1.5%
Nagarmotha root	*Motha*	Extract	*Cyperus rotundus* Linn.	1.5%
Harsinghar stem	*Harsinghar*	Extract	*Nyctanthes arbortristis* Linn.	1.5%
Anzroot	*Anjira*	Extract	*Astragalus sarcocolla* Dymock.	1.5%
Sibr	*Ghee kuar*	Extract	*Aloe barbadensis* Mill.	3%
Baboona	*Banune-ke-phool*	Essential oil	*Matricaria chamomilla* Linn.	0.5%
Khus	*Khas*	Essential oil	*Vetiveria zizanoides* (Linn.) Nash.	0.3%
Mur-makki	*Bol / Mur*	Essential oil	*Commiphora myrrha* (Nees) Engl).	0.2%
Kundur	*Gugal / Luban*	Essential oil	*Boswellia serrata* Roxb.	0.2%
Chameli	*Chambeli / Madhumalti*	Essential oil	*Jasminum officinalis* Linn.	0.3%
Badam	*Badam*	Fixed oil	*Prunus dulcis* var.*dulcis* (D.C) Buchheim.	5%
Zaitoon	*zaytoun*	Fixed oil	*Olea europaea* Linn.	5%
Safaida kashghari	*Putty*	Powder	Zinc oxide	1.5%
Cream base		Cream	-	Q.S.

of the test formulations were mixed at the step while mixing of the aqueous solution with the oily phase of the cream base. After that all the essential oils of the test formulations were mixed finally into the cream material with uniform stirring using mechanical stirrer. The formulated cream was kept into the small packs made up of food grade plastic. The following schedule was adopted in the control and test group in the Acne vulgaris patients: In control group, cream base topically on face twice a day and in test group, UHC topically on face twice a day. The severity of acne vulgaris was assessed on the basis of the Investigator's Global acne severity score (Table 3). All statistical calculations were made using Graph Pad InStat of Graph Pad Software Inc, San Diego, USA. Two statistical tests, ANOVA and Paired t- test were performed for within group comparisons and inter group comparisons, respectively.

Table 2—Composition of cream base

Ingredients	Proportion
Stearic acid	20 gm
Potassium hydroxide	3 gm
Cetostearyl alcohol	7 gm
Bees wax (white)	5 gm
Triethanolamine	1.5 gm
Glycerine	5 gm
Methyl paraben sodium	200 mg
Propyl paraben sodium	200 mg
Liquid paraffin	6 gm
Lanolin	2 gm
Petroleum jelly	4 gm
Purified water	100 ml

Table 3—Investigator's global acne Severity Score

Score	Description of acne
0	Clear; no inflammatory lesions
0.5	Sparse comedones, with very few or no inflammatory lesions present
1.0	Comedones, with some small inflammatory lesions present; minimal erythema
1.5	Comedones, with an increasing number of inflammatory lesions compared to grade 1
2.0	Comedones, with a moderate number of small inflammatory lesions extending over a wide area of the face; increasing erythema
2.5	Comedones, with an increasing number of inflammatory lesions vs. grade 2.0, with some larger inflamed lesions
3.0	Numerous comedones, papules, and pustules with larger inflamed lesions extending over much of the face; erythema may be pronounced
3.5	Comedones, with profuse papulopustular lesions with numerous large inflammatory lesions; some deep pustular lesions may be present
4.0	Patient has severe or cystic (nodular) acne and is excluded from the study

Results

The statistical analysis (ANOVA) (Tables 4-7) of the results of different stages of treatment of Acne vulgaris with plain cream base shows that the scores of the severity at baseline phase (column A) was 3.150 ± 0.1302 (mean ± standard error) (P >0.10); on 15th day (column B) it was 3.150±0.1302 (P >0.10); on 30th day (column C) it was 2.700±0.1333 (P >0.10); on 45th day (column D), it was 2.350±0.1067 (P >0.10), while on

Table 4—*Tukey-Kramer* multiple comparison test (Acne vulgaris – control group)

Comparison	Mean difference	Q	*P* value
Column A vs Column B	0.000	0.000	ns P >0.05
Column A vs Column C	0.4500	3.688	ns P >0.05
Column A vs Column D	0.8000	6.556	***P<0.001
Column A vs Column E	1.000	8.195	***P <0.001
Column B vs Column C	0.4500	3.688	ns P >0.05
Column B vs Column D	0.8000	6.556	***P <0.001
Column B vs Column E	1.000	8.195	***P <0.001
Column C vs Column D	0.3500	2.868	ns P >0.05
Column C vs Column E	0.5500	4.507	* P <0.05
Column D vs Column E	0.2000	1.639	ns P >0.05

A: Baseline phase; Treatment phase: B (15th day), C (30th day), D (45th day), E (60th day)

Table 5—Assumption test (Acne vulgaris – control group)

Group	KS	*P*. value	Passed normality test
Column A	0.3024	>0.10	Yes
Column B	0.3024	>0.10	Yes
Column C	0.3616	>0.10	Yes
Column D	0.2716	>0.10	Yes
Column E	0.2716	>0.10	Yes

Table 6—Intermediate calculations (ANOVA) (Acne vulgaris – control group)

Source of variation	Degree of freedom	Sum of squares	Mean square
Treatment (between columns)	4	8.300	2.075
Residuals (within columns)	45	6.700	0.1498
Total	49	15.000	

F =n 13.937 (MS treatment/MS residual)

Table 7—Summary of data - ANOVA
(Acne vulgaris – control group)

Group	No of points	Mean	Standard deviation	Standard error of mean	Median
Column A	10	3.150	0.4116	0.1302	3.250
Column B	10	3.150	0.4116	0.1302	3.250
Column C	10	2.700	0.4216	0.1333	3.000
Column D	10	2.350	0.3375	0.1067	2.500
Column E	10	2.150	0.3375	0.1067	2.000

Group	Minimum	Maximum	95% confidence interval	
			From	To
Column A	2.500	3.500	2.856	3.444
Column B	2.500	3.500	2.856	3.444
Column C	2.000	3.000	2.398	3.002
Column D	2.000	3.000	2.109	2.591
Column E	1.500	2.500	1.909	2.391

A: Baseline Phase; Treatment Phase: B (15th day), C (30th day), D (45th day), E (60th day)

Table 8—*Tukey-Kramer* multiple comparison test
(Acne vulgaris – test group)

Comparison	Mean difference	Q	*P* value
Column A vs Column B	0.5000	5.872	***P <0.001
Column A vs Column C	1.025	12.038	***P <0.001
Column A vs Column D	1.625	19.085	***P <0.001
Column A vs Column E	2.075	24.370	***P <0.001
Column B vs Column C	0.5250	6.166	***P <0.001
Column B vs Column D	1.125	13.212	***P <0.001
Column B vs Column E	1.575	18.497	***P <0.001
Column C vs Column D	0.6000	7.047	***P <0.001
Column C vs Column E	1.050	12.332	***P <0.001
Column D vs Column E	0.4500	5.285	***P <0.001

A: Baseline phase; Treatment phase: B (15th day), C (30th day), D (45th day), E (60th day)

60th day (column E) of treatment phase was 2.150 ± 0.1067 (P >0.10). Comparisons of different columns were also made and it was observed that the columns A and D, A and E, B and D, B and E showed very significant differences of means (P <0.001). The column C and E showed significant difference of means (P <0.05). The column A and B, A and C, B and C, C and D and D and E showed that the differences were not significant (P >0.05).

Table 9—Assumption test (Acne vulgaris – test group)

Group	KS	*P*. value	Passed normality test
Column A	0.2250	>0.10	Yes
Column B	0.2250	>0.10	Yes
Column C	0.2233	>0.10	Yes
Column D	0.2803	0.0864	Yes
Column E	0.3274	0.0275	No

Table 10—Summary of data - ANOVA
(Acne vulgaris –test Group)

Group	No of points	Mean	Standard deviation	Standard Error Of mean	Median
Column A	20	2.975	0.4128	0.09230	3.000
Column B	20	2.475	0.4128	0.09230	2.500
Column C	20	1.950	0.3940	0.08811	2.000
Column D	20	1.350	0.3663	0.08194	1.500
Column E	20	0.9000	0.3078	0.06882	1.000

Group	Minimum	Maximum	95% confidence interval	
			From	To
Column A	2.500	3.500	2.782	3.168
Column B	2.000	3.000	2.282	2.668
Column C	1.500	2.500	1.766	2.134
Column D	1.000	2.000	1.179	1.521
Column E	0.5000	1.500	0.7559	1.044

A: Baseline phase; Treatment phase: B (15th day), C (30th day), D (45th day), E (60th day)

The statistical analysis (ANOVA) of the results (Tables 8-10) of different stages of treatment of Acne vulgaris with UHC shows that the scores of the severity at baseline phase (column A) was 2.975 ± 0.0923 (mean ± standard error) (P >0.10); on 15th day (column B), it was 2.475 ± 0.0923 (P >0.10); on 30th day (column C), it was 1.950 ± 0.08811 (P >0.10); on 45th day (column D), it was 1.350 ± 0.08192 (P=0.0864). While on 60th day (column E) of treatment phase was 0.9000 ± 0.06882 (P=0.0275). Comparisons of different columns were also made and it was observed that the columns A and B, A and C, A and D, A and E, B and C, B and D, B and E, C and D, C and E showed very significant differences of

Table 11—Severity of acne vulgaris at baseline phase (Paired *t*-test - summary of data)

Parameters	Column A*	Column B**	Difference
Mean	3.150	2.975	0.4500
# of points	10	20	10
Std. deviation	0.4116	0.418	0.4972
Std. error	0.1302	0.09230	0.1572
Minimum	2.500	2.500	-0.5000
Maximum	3.500	3.500	1.000
Median	3.250	3.5000	0.5000
Lower 95% CI	2.856	2.782	0.09434
Upper 95% CI	3.444	3.168	0.8057

Two tailed p value is 0.0187, considered signicant
T = 2.862 with 9 degrees of freedom
*Control group; **test group

Table 12—Severity of Acne vulgaris at 15th day of Treatment Phase (Paired *t*-test -summary of data)

Parameters	Column A*	Column B**	Difference
Mean	3.150	2.475	0.9500
# of points	10	20	10
Std. deviation	0.4116	0.4128	0.4972
Std error	0.1302	0.09234	0.1572
Minimum	2.500	2.000	0.000
Maximum	3.500	3.000	1.500
Median	3.250	2.500	1.000
Lower 95% CI	2.856	2.282	0.95943
Upper 95% CI	3.444	2.668	1.306

Two tailed *p* value is 0.0002, considered extremely significant
T = 6.042 with 9 degrees of freedom
*Control group; **test group

Table 13—Severity of acne vulgaris at 30th day of treatment phase (Paired *t*-test -summary of data)

Parameters	Column A*	Column B**	Difference
Mean	2.700	1.950	1.000
# of points	10	20	10
Std. deviation	0.4216	0.3940	0.5270
Std. error	0.1333	0.08811	0.1667
Minimum	2.000	1.500	0.000
Maximum	3.000	2.500	1.500
Median	3.000	2.000	1.300
Lower 95% CI	2.398	1.766	0.6230
Upper 95% CI	3.002	2.134	1.377

Two tailed p value is 0.0002, considered extremely significant
T = 6.000 with 9 degrees of freedom
*Control group; **test group

means (P <0.001). While the column D and E showed that the difference is also significant. The inter group comparisons using paired *t*-test of baseline phase (Table 11) showed that the severity of Acne vulgaris was 3.150 ± 0.1302 (mean ± standard error) in control group (column A); while it was 2.975 ± 0.0923 in the test group (column B). The two-tailed P value is 0.0187 that is considered significant. The inter group comparisons using paired *t*-test of 15th day of treatment phase (Table 12) showed that the severity of Acne vulgaris was 3.150 ± 0.1302 (mean ± standard error) in control group (column A); while it was 2.475 ± 0.0923 in the test group (column B). The two tailed P value is 0.0002 that is considered extremely significant. The inter group comparisons using paired *t*-test of 30th day of treatment phase (Table 13) showed that the severity of Acne vulgaris was 2.700 ± 0.1333 (mean ± standard error) in control group (column A); while it was 1.950 ± 0.08811 in the test group (column B). Two tailed P value is 0.0002 that is considered extremely significant. The inter group comparisons using paired *t*-test of 45th day of treatment phase (Table 14) showed that the severity of Acne vulgaris was 2.350 ± 0.1067 (mean ± standard error) in control group (column A); while it was 1.350 ± 0.08192 in the test group (column B). Two tailed P value is <0.0001 that is considered extremely significant. The inter group comparisons using paired *t*-test of 60th day of treatment phase (Table 15) showed that the severity of acne vulgaris was 2.150 ± 0.1067 (mean ± standard error) in control group (column A); while it was 0.9000 ± 0.06882 in the test group (column B). The two-tailed P value is <0.0001 that is considered extremely significant.

Discussion

It is evident that the above results and observations of UHC has proved effective in the treatment of Acne vulgaris, it might be due to anti-inflammatory, resolvent, detergent, soothing, emollient, wounds healing and antiseptic drugs present in the compound formulation. The efficacy of the ingredients of UHC mentioned in the Unani classical literature as *Irsa* and *Baboona* is a good anti-inflammatory, resolvent and detergent, it cleanses the secretions and debris of the wound and produces new tissues, make them dry, improve local circulation and resolve thick secretions. *Neem* cleanses wounds due to antiseptic property, *Nagarmotha* is antiinflammatory, antiseptic, wounds healing and resolvent, and acts as a healing agent on

Table 14—Severity of acne vulgaris at 45th day of treatment phase (Paired *t*-test -summary of data)

Parameters	Column A*	Column B**	Difference
Mean	2.350	1.350	1.300
# of points	10	20	10
Std deviation	0.3375	0.3663	0.4216
Std error	0.1067	0.08192	0.1333
Minimum	2.000	1.000	0.5000
Maximum	3.000	2.000	2.000
Median	2.500	1.50	1.500
Lower 95% CI	2.109	1.179	0.9984
Upper 95% CI	2.599	1.51	1.602

Two tailed p value is <0.0001, considered significant
T = 9.750 with 9 degrees of freedom
*Control group; **test group

Table 15—Severity of acne vulgaris at 60th day of treatment phase (Paired *t*-test - summary of data)

Parameters	Column A*	Column B**	Difference
Mean	2.150	0.9000	1.450
# of points	10	20	10
Std. deviation	0.3375	0.3078	0.4378
Std. error	0.1067	0.06882	0.1384
Minimum	1.500	0.5000	0.5000
Maximum	2.500	1.500	2.000
Median	2.000	1.000	1.500
Lower 95% CI	1.909	0.7559	1.137
Upper 95% CI	2.391	1.044	1.763

The two-tailed p value is <0.0001, considered significant
T = 10.474 with 9 degrees of freedom
*Control group; **test group

external and internal use, its also mentioned as detergent and ruberfacient. *Aloe* is antiseptic, emollient, bactericidal, and fungicidal while *Khus is* reported as refrigerant, detergent and antiseptic drug in the classical Unani books. The analyzed results showing very significant effects of UHC in Acne vulgaris is attributed to its ingredients like *Irsa, Neem, Harsingar, Anzaroot,* etc.

Conclusion

The Unani herbomineral cream has been proved to be effective in the treatment of Acne vulgaris in human beings. It is also an approval of the Unani approaches of treatment of Acne vulgaris as already revealed from the Unani literature. Therefore, the formula of Unani herbomineral cream may be put forward for further detailed investigations and larger multi-centric clinical trials for its further approval as an effective remedy of Acne.

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