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Clinical Efficacy of Unani formulae in the Management of Nazla Haar (Allergic Rhinitis)

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Abstract: *Nazla Haar* is a condition with watery irritating nasal discharge dripping down towards throat, with burning sensation in nose, face, eyes with lacrimation, and also alters the sense of olfaction. The similar features resemble rhinitis in modern, which of various etiopathogenesis, mostly of allergic origin. Allergic rhinitis (AR) is characterized by sneezing, nasal congestion, nasal itching and nasal discharge and is caused by immunoglobulin E (IgE)-mediated reactions to inhaled allergens. AR is one of the most common chronic conditions in high-income countries, with a prevalence of up to 50% in some countries. The objective of the study was to evaluate the efficacy of Unani formulae in the management of Allergic rhinitis. A randomized single blinded placebo controlled study was conducted over 40 patients (test =30 and placebo =10). The test group was given decoction of *Behidana*, *Unnab* and *Sapistan* with *Sharbat e Banafsha*, whereas, the placebo group was treated with caramel syrup. Both groups were received drugs in a dosage of 25 ml twice a day for 15 days. The efficacy of the study was assessed by observing both subjective and objective parameters in three follow ups, on four point scale. Total Symptom Severity Score (TSSS), and the overall response was assessed by using statistical tests like Paired and Kruskal- Wallis with Dunn's Multiple Comparison. Test drug was found to be effective with P<0.01 in comparison with placebo. From the results and observations it can be concluded that the test formulae is effective in reducing the symptoms of allergic rhinitis, however, to make the study more comprehensive it could be conducted in large sample size in multi centres on various parameters.

Key words: *Nazla Haar*, Allergic rhinitis, Unani formulae, placebo, nasal smear for eosinophil, quality of life.

I Introduction

Nazla Haar is a condition with watery irritating nasal discharge dripping down towards throat, with sense of burning (*sozish*) in nose, face and eyes with lacrimation, and also alters the sense of olfaction (Ismail, 2010). The similar features resemble rhinitis in modern, which of various etiopathogenesis, mostly of allergic origin. Allergic diseases such as asthma, urticaria and eczema including rhinitis have been known for centuries, and their history dates back to antiquity (Azizi, 2010). Allergic rhinitis (AR) is characterized by sneezing, nasal congestion, nasal itching and nasal discharge and is caused by immunoglobulin E (IgE)-mediated reactions to inhaled allergens (Bousquet et al, 2020). Common allergens are pollen of grasses, weed and trees, house-dust mites, animal dander mold and foods. Exposure to an allergen triggers the release of histamine which causes the inflammatory reaction and onset of symptoms (Fazeenah and Quamri, 2015). These immune reactions involve mucosal inflammation that is driven by type 2 cells. Further, allergic rhinitis seems to be the consequence of environmental exposures acting on a predisposed genetic background. AR is often co-morbid with asthma and/or conjunctivitis (Bousquet et al, 2020).

AR is one of the most common chronic conditions in high-income countries, with a prevalence of up to 50% in some countries. AR is a worldwide health problem that causes major concern and disability globally, and it contributes to affect the quality of life by lost or nonproductive time at work, school and in children, reduced engagement in outside activities. The economic effect of AR is often underestimated as indirect costs are substantial, but the effect of AR on work productivity is estimated to cost €30 billion to €50 billion per year in the European Union (Bousquet J 2020).

Unani system of medicine considered allergic rhinitis as a disease with multiple etiologies; accordingly it was treated with holistic approach by adopting the principles of contrary to the disease state. Based on the range of prescriptions comprises on single and compound formulae for the management of allergic rhinitis, the present formulae from *Bayaze Kabeer* were selected to validate clinically its safety and efficacy in allergic rhinitis, which consists of decoction of *Behidana* (*Cydonia oblonga*), *Unnab (Zizyphus jujube)* and *Sapistan (Cordia dichotoma)* with *Sharbate Banafsha (Viola odorata)*.

The different pharmacological effects of the drugs like anti catarrh, soothing, demulcent, heat reducing agent, astringent, deobstruent, concoctive for thick humors, expectorant, anti inflammatory, neutralizer, moisturizer, and sedative of various ingredients are in the test formulae mentioned above. The aim of this study was to assess the efficacy of the Unani formulae in the management of allergic rhinitis.

II MATERIALS AND METHODS

This clinical study was a randomized single blinded placebo study, which was conducted at National Institute of Unani Medicine (NIUM), hospital Bengaluru after the approval of the Institutional Ethical Committee (IEC) 2010/'11, over a period of nine (09) months in 2011. Forty (40) patients between 12 to 50 years of age from both gender were enrolled in the study and they were randomly allocated in to two as test (n=30) and placebo (n=10) groups. Patients with typical history with clinical features of *Nazla Haar*, and who have agreed to follow the protocol of the study, were included after obtaining their written informed consent. At the same time, patients with complications of allergic rhinitis, atrophic rhinitis, chronic sinusitis, nasal septum deviation, nasal polyps or growths, asthma, history of allergic to aspirin, and patients with systemic diseases like diabetes mellitus, cardiovascular, impaired renal and hepatic functions and who were on steroid therapy were excluded from the study.

The Test group was treated by a Unani formulae, which consists of a decoction and a syrup. The decoction contains coarse powders of *Cydonia oblonga (Behdana)*, *Zyziphus jujuba* (*Unnab*), *Chordia dichotoma (Sapistan)* and the syrup contains flowers of *Viola odorata (Banafsha)* and sugar. The dosages of the decoction and the syrup were each 25ml twice a day orally, after meals for 15 days. The placebo group was treated with caramel syrup, with the same quantity and the same duration. The evaluation of efficacy was based on the subjective parameters such as rhinorrhoea, sneezing, nasal congestion and itchy nose were carried out on baseline (0^{th} day), 4^{th}, 8^{th} and 15^{th} day, while the objective parameter 'Nasal Smear for Eosinophils (NSFE)' was observed on baseline and on 15^{th} day at the end of the treatment.

After 15 days of treatment, the pre and the post treatment data were analyzed and subjected to comparison statistically to evaluate the efficacy and safety of the treatment. In order to determine the adverse effect of test drug, safety parameters like haemogram, LFT and RFT were carried out, which were found within the normal limits.

The diagnosis had been established on the basis of the history, findings on physical examination and the laboratory investigations.

Sample of nasal secretion was collected by a tightly wound cotton swab from the posterior part of the lower or middle turbinate (Crobach et al, 1996). Then the smear was spread out to a thin layer on a glass slides, stained by diluted Giemsa solution (1ml Giemsa stain was diluted by 9 ml of distilled water), and kept them for air dry. Then, the stained slides were observed under the electronic microscopy in different powers for eosinophils. For this single-blinded, placebo controlled study, all the smears were coded and read by a single investigator. Grading of nasal smear was done by using method of Shioda H and Mishima T (Table -1).

Table 1: Grading of nasal smear Shioda H 1966

Severity	Results
0	No cells
+	Few cells or small clumps
++	Moderate number or large clumps
+++	Large clumps

Statistical analysis

Data were analyzed by using Paired and Kruskal- Wallis with Dunn's Multiple Comparison.

III RESULTS

Total 40 patients completed the study. The basic characteristics of the patients are shown in Table-2.

Table-2: Basic Characteristics of Research Subjects

Characteristics	Test Group (n=30)	Placebo Group (n=10)
Age (mean ± SEM)	29.6 ± 3.39	29.86 ± 1.83
Sex: Male Female	19 11	06 04
Dietary pattern: Vegetarian Non vegetarian	01 29	03 07
Socio economic status: Upper Middle Lower	 02 27 01	 01 08 01
Family History: Positive Negative	 09 21	 03 07
Occupation: Student Businessman Teacher House wife Tailor Mechanic Other	09 03 04 03 04 02 05	01 04 00 04 00 01 00
Duration of diseases in years (mean ± SEM)	3.82 ±0.66	3.57 ± 1.20
Seasonal variation: Seasonal Perennial	17 13	05 05
Effect of allergens: Dust Dust + Cold Dust + Smoke Others	 11 10 05 04	 03 07 00 00

A positive nasal smear for eosinophils was identified in 26 patients (86.67%) in the test group and only 5 (50%) in controls (Table 3). The difference between the test and control groups was statistically significant ($p < 0.05$). Incidence of eosinophils was found to increase in smears with increasing severity of sneezing and runny nose. It was significantly higher in patients with complaints of intermittent as compared to continuous nasal symptoms.

Table 3: Grading of Nasal Smear for Eosinophils in allergic rhinitis patients (n=40)

Grading of NSFE	Test group (n=30)	Placebo group (n=10)
0	4	5
+	18	3
++	5	2
+++	3	0
Total	30	10

Table 4: Numbers of patients with subjective symptoms (n=40)

Subjective Parameters	Number of subjects remain positive on assessment day							
	Test group (n=30)				Placebo (n=10)			
	0th day	4th day	8th day	15th day	0th day	4th day	8th day	15th day
Rhinorrhoea	26	22	13	5	10	10	10	7
Sneezing	27	20	14	6	9	9	9	8
Nasal congestion	26	16	6	2	10	9	9	9
Itchy nose	16	8	3	1	6	5	5	4
Itchy mouth or throat	17	11	6	1	4	2	3	3
Lacrimation	22	10	7	1	6	4	5	5
PND	15	8	4	1	6	5	6	4
Headache	17	8	4	3	5	5	4	4

The effect of the study was assessed in each follow ups for both groups and was compared by using Friedman test for intra-group comparison and Kruskal-Wallis test with Dunn's multiple comparison pair tests for inter-group comparison. The test group has shown very significant reduction ($p<0.01$) in the severity of subjective parameters like rhinorrhoea, sneezing, nasal congestion, itchy nose, mouth or throat, lacrimation, post nasal drip and headache, while placebo control group remained insignificant till 15th day of treatment Table 5.

Table 5: Effect of study on subjective parameters (Mean±SEM and Median rating with range in brackets)

Subjective parameters	Test group (n=30)				Placebo control group (n=10)			
	0th day	**4th day**	**8th day**	**15th day**	**0th day**	**4th day**	**8th day**	**15th day**
Rhinorrhoea	2.1±0.2 2.5{0,3}	1.3±0.2 1{0,3}	0.6±0.15 0{0,3}[a]	0.26± 0.13 0{0,3} [a]	1.4 ±0.22 1{1,3}	1.4±0.22 1{1,3}	1.5±0.22 1{1,3}	0.9±0.2 3 1{0,2}
Sneezing	2.2±0.2 3{0,3}	1.13±0.2 1{0,3}[a]	0.6±0.15 0{0,3}	0.26±0.12 0{0,3} [b]	1.7±0.33 1.5{0,3}	1.7±0.33 1.5{0,3}	1.4±0.3 1{0,3}	1.1±0.2 7 1{0,3}
Nasal congestion	1.8±0.2 2{0,3}	0.8±0.2 1{0,3}[a]	0.3±0.1 0{0,2}	0.1±0.07 0{0,2} [b,c]	1.4±0.3 1.5{0,3}	1.4±0.3 1{0,3}	1.1±0.2 1{0,2}	0.7±0.2 1{0,2}
Itchy nose	0.6±0.12 1{0,2}	0.3±0.09 0{0,2}	0.1±0.05 0{0,1} [a]	0.03±0.03 0{0,1} [a, b]	0.7±0.21 1{0,2}	0.6±0.22 0.5{0,2}	0.5±0.16 0.5{0,1}	0.4±0.1 6 0{0,1}
Itchy mouth	0.6±0.11 1{0,2}	0.36±0.08 9 0{0,1}	0.2±0.07 0{0,1} [a]	0.03±0.03 0{0,1}	0.4±0.16 0{0,1}	0.2±0.13 0{0,1}	0.3±0.15 0{0,1}	0.3±0.1 5 0{0,1}
Lacrimation	0.93±0.14 1{0,3}	0.36±0.10 0{0,2} [a]	0.23±0.0 7 0{0,1}	0.03±0.03 0{0,1}	0.6±0.16 1{0,1}	0.5±0.22 0{0,2}	0.5±0.16 0.5{0,1}	0.5±0.1 6 0.5{0,1}
PND	0.66±0.15 0.5{0,3}	0.26±0.09 0{0,2}	0.10±0.0 5 0{0,1}	0±0.00 0{0,0} [a, b, c]	1.00±0.3 6 1{0,3}	0.70±0.3 0 0.5{0,3}	0.8±0.29 1{0,3}	0.6±0.3 1 0{0,3}
Headache	0.73±0.14 1{0,2}	0.33±0.12 0{0,3}	0.17±0.0 8 0{0,2} [a]	0.13±0.07 0{0,2} [a]	0.6±0.22 0.5{0,2}	0.5±0.17 0.5{0,1}	0.4±0.16 0{0,1}	0.5±0.2 2 0{0,2}
a-p<0.001at 0th day of test; b-p<0.05 at 4th day test; c-p<0.05 at 8th day of placebo								

The objective parameter NSFE was analyzed by using Kruskal-Wallis test with Dunn's multiple comparison pair tests for inter-group. Test group exhibited highly significant ($p<0.001$) with marked reduction in subjective symptoms comparison to placebo control, which has shown no significant changes Table 6.

Table 6: Effect of study on objective parameter-NSFE

Groups	Nasal Smear for Eosinophils	
	Before treatment	After treatment
Test Group (n=30)	1.73±0.13 2{0,2}	0.03±0.09 [a] 0{0,1}
Placebo Control Group (n=10)	1.00±0.33 1{0,2}	0.8±0.33 0{0,2}
a-p<0.001 with respect to test before treatment		

The overall effect of the study was determined based on the Total Symptoms Severity Score (TSSS) of Mean ± SEM of subjective parameters. The TSSS in test group before treatment was 9.60 ±0.64 and 0.90±0.32 after treatment, whilst it was 7.80±1.03 and 5.00±0.94 respectively in placebo group. When the Mean ± SEM of TSSS in both groups were compared statistically by using Paired't' test for intra group, and Kruskal–Wallis with post Dunn's Multiple Comparison tests for inter-group and it was observed that the test group found very significant with p value <0.01 after the treatment when compared with placebo and test before treatment.

In test group out of 30 patients 28 (93.33%) were found < 2 TSSS along with negative eosinophils, whilst, the placebo group patients were remained positive eosinophils along with marginal reduction in TSSS without significant change in eosinophils (Table 7).

Table 7: Overall Effect on the study Based on TSSS and NSFE (n=40)

Groups	Sample Size	Before Treatment			After Treatment		
		NSFE (+)	NSFE (-)	TSSS (Mean)	NSFE (+)	NSFE (-)	TSSS (Mean)
Test Group	30	26	4	9.6	1*	4	0.9
Placebo Control Group	10	5	5	7.8	5	5	5.0
Total	40	31	9	17.4	5	9	5.9

* Significantly reduced in numbers.

Moreover, the effect of the study determined in terms of CURE and NOT CURE is based on the difference of TSSS individual subjective symptoms score along with the effect on NSFE before treatment was compared with after treatment (Table 8), those found to be between 0 - ≤ 2 with negative or significant reduction in the number of NSFE is considered as **"cure"**, whereas, any change of TSSS with > 2 or remain unchanged along with no significant reduction or presence of eosinophils is considered as "**not cure"**.

Table 8: Overall Effect on the Study in terms of Response

Effect	Test Group	Placebo	Response in Toto
Cure	28	00	28*
Not Cure	02	10	12
Total	30	10	40

*Fisher's exact test 2 tailed P<0.001

Out of 30 patients, only 26 in test and 5 out of 10 in placebo groups were positive with nasal smear for eosinophils before start the treatment. After the day 15, only 1 patient's NSFE was found in test group mild positive with reduction in number in comparison to baseline, and in control group all the 5 patients' NSFE were remained as same. On statistical analysis by Kruskal-Wallis with Dunn's Multiple Comparison Pair tests, the test group exhibited highly significant (p<0.001) effect on NSFE after the treatment when compared with the baseline before treatment, whereas in placebo control group no significant changes in NSFE was observed (Table 7 and Figures 1 & 2) respectively.

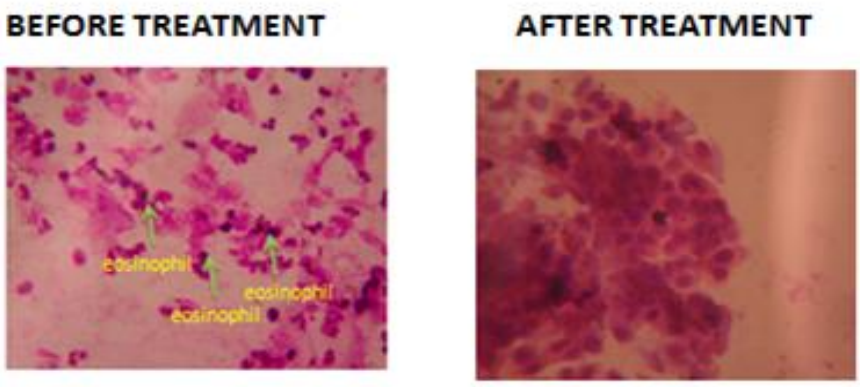

Fig: 1-Nasal smear with Giemsa stain (10 x) in test group

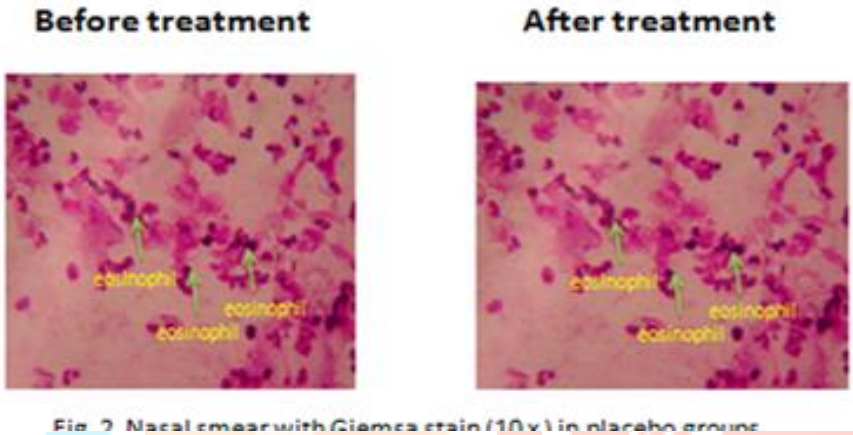

Fig: 2 -Nasal smears with Giemsa stain (10 x) in placebo group

V. DISCUSSION

In this study, it was established that the Unani formulae were effective in the management of allergic rhinitis by eliminating or eradicating the oesinophils from the nasal smear. The formulae consists of Cydonia oblonga, Zizyphus jujube, Cordia dichotoma and Viola odorata possess pharmacological properties of to reduce post nasal drip, exhilirant, demulcent, anti inflammatory, blood purifier, expectorant, viscosity, cooling and sedative (Kabiruddin, 2007).

The nasal smear for eosinophil (NSFE) is a good diagnostic tool for allergic rhinitis. Nasal cytology has been performed previously and reported using different specimen sources and different staining techniques. Miller et al determined the diagnostic value of eosinophils in nasal secretion by Hansel's stain and found sensitivity and specificity 70% and 94% respectively (Jirapongsananuruk and Vichyanond, 1998).

The beneficial effect of test formulae is due to its chemical constituents. The ***Behidana*** (*Cydonia oblonga* Miller) from Rosaceae familyis is the seeds of *Behi* (Quince). The fruit contains pectin that similar to apple and the fruit juice contain thiamine, riboflavin, nicotinic acid, vitamin B6, inositol, pantothenic acid, folic acid and biotin (Fazeenah and Quamri, 2016). Shinomiya et al. (2009) studied the anti allergic effect of hot water extract of quince fruit in mice, and Huber et al. (2012) investigated the immunomodulatory and anti allergic properties from phenolic compounds of Citrus and Cydonia fruits in patients suffering from allergic disorders, and compared with azelastine and dexamethasone. The results showed that the degranulation of basophilic cells diminished only in the presence of Citrus, further, both Cydonia and Citrus together inhibited the production of IL-8 and TNF-α from human mast cells. Benkhadir et al. (2012) investigated the anti inflammatory effect of a polyphenolic extract of Quince peel against Lipopolysaccharide (LPS) induced inflammation in human. Further Cydonia oblonga has an inhibitory effect on broad range of the late phase immune reactions of mast cells (Kawahara and Zuka, 2011).

Unnab *(Zizyphus jujuba* Mill), also known as Red date or Chinese date belongs to family Rhamnaceae. The jujuba fruits shown to produce anti-inflammatory, anti-obesity, immune-stimulating, antioxidant, gastrointestinal and hepatoprotective effect and inhibit foam cell formation in macrophages (Naika et al, 2013), also it possesses anti allergic property (Su et al, 2000, Al Reza et al, 2010). Another study showed that the mice with ovalbumin (OVA)-induced allergic rhinitis, cAMP reduced the secretion of IgE and histamine in the plasma, demonstrated that the jujube suppressed cytokine production in the allergic response pathway, which resulted in prevention or alleviation of allergy symptoms (Jiang et al, 2019). Further, it is reported that the anti-oxidant and immunological activities of polysaccharides isolated from Ziziphus jujuba and it was evaluated the anti-influenza activity of betulinic acid isolated from methanolic extract of root of *Zizyphus jujuba* (Ansari et al, 2020).

Sapistan *(Cordia dichotoma)* has analgesic, anti-inflammatory, expectorant and hepatoprotective properties (Kuppast and Nayak, 2006, Sharma et al, 2010). A study showed that the immunomodulary effect of alcoholic (70%) extract of *Cordia dichotoma* fruit with reference to significant increase in the total leucocyte count in rats and another study revealed that the extract of *Cordia dichotoma* plant has relaxant activity on tracheal smooth muscles in sheep. The possible mechanism of action may be the stimulation of nitric oxide synthesis (Ansari et al, 2020).

Banafsha (Viola odorata L. from Violaceae family)is commonly called as sweet violet and is well known to India for its medicinal virtues and has been in use since olden times for treating several diseases both in Unani and in Ayurvedic systems of medicine (Fazeenah and Quamri, 2020). Banafsha has shown various medical applications due to the composition of flavonoids, saponins, and alkaloids (Feyzabadi et al, 2017), similarly the aqueous extract of *Viola odorata* has anti-inflammatory property equal to corticosteroids in the treatment of inflammatory conditions of the lung (Koochek et al, 2003). Koochek M.H., et al. (2002) investigated anti-inflammatory property of an aqueous extract of Viola odorata compared with hydrocortisone and the study showed that the aqueous extract of V. odorata proved to be as effective anti-inflammatory as hydrocortisone in the treatment of formalin induced inflammation of lung tissues and safer medicinal agent than corticosteroids in treatment of inflammatory conditions of the lung. Antil V., et al. (2011) investigated the crude methanolic extract at the dose of 400 mg/kg of Viola odorata was proved analgesic in acetic acid induced writhing and tail immersion animal models.

VI. CONCLUSION

The study evidences from the results and observations that test group showed good response; in the light of above discussion it can be concluded that the test drug is effective in reducing the symptoms of allergic rhinitis, therefore, it can be used effectively and safely in it management. However, to make the study more comprehensive it could be conducted in large sample size in multi centers on various parameters.

VII. ACKNOWLEDGEMENT

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