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Research Article

SINGLE-BLIND, RANDOMIZED, CONTROL TRIAL OF A UNANI COMPOUND FORMULATION IN ILTEHAB TAJAWEEFE ANAF MUZMIN

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ABSTRACT

Objective: The objective of the study was to establish the efficacy and tolerability of oral Unani formulations with inhalation of Kalonji and to provide safe, effective, and economical treatment for Iltehab Tajaweefe Anaf Muzmin (chronic rhinosinusitis [CRS]).

Methods: A randomized single-blind, comparative study of 40 patients of CRS. The patients were randomly allocated to two groups each consisting of 20 patients. In Group A, oral Unani formulation of Katan (*Linum usitatissimum*), Filfil Siyah (*Piper nigrum*), and honey was given 6 g BD with steam inhalation of Kalonji (*Nigella sativa*) and Tab Alaspan 1 BD with Karvol Plus inhalation was given in Group B.

Results: Statistical analysis of the data was done using paired t test by comparing the visual analog scale score of all major and minor symptoms before and after treatment. The result is statistically highly significant in Group A ($p<0.0001$) and it is significant in Group B. ($p<0.01$).

Conclusion: It may be concluded that the oral Unani formulation with inhalation of Kalonji has statistically highly significant effect on major and minor symptoms of CRS. A multicentric trial of the test drug on larger sample size for a longer duration is required to establish the efficacy of the formulation on CRS.

Keywords: Chronic rhinosinusitis, Unani formulation, Katan, Kalonji inhalation.

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INTRODUCTION

Chronic rhinosinusitis (CRS) is the inflammation of the nose and paranasal sinuses. It is a very commonly occurring disease; adversely affecting the health of the population world over. It significantly impacts the quality of life even in comparison to chronic debilitating diseases such as diabetes mellitus and congestive heart failure. CRS is not only causing significant physical symptoms but it also results in substantial functional and emotional impairment.

CRS is one of the most common health care problems globally, and the incidence of CRS appears to be increasing yearly.

In the US as per an earlier estimate by American Academy of otolaryngology, more than 37 million Americans have at least one episode of CRS in a year, which lasts for more than 8–12 weeks and can significantly affect the worker's productivity and school performance on an individual level.

In a recent study, it has been concluded there was a loss of a total of 21.2 household days per year due to daily sinus care requirement with an annual productivity cost of $10,077.07 per patient in the USA [1].

In India, the National Institute of Allergy and Infectious Disease has estimated that about 134 million Indians are suffering from CRS [2].

Standard medical therapy of CRS includes both a broad-spectrum antibiotic and a topical intranasal steroid to address the strong inflammatory component of this disease. Local decongestants and mucolytic agents as nasal drops and antihistamines are also recommended as adjunctive therapy as per the need of the patient. In some cases, the cavities are so clogged that surgery is recommended [3]. However, revision surgeries were required in 20% cases [4]. The potential side effects of the above-mentioned regimen with long-term usage such as drug resistance, allergic reactions, and altered normal flora of the intestine are also of concern. Seemingly, all these and many other such reasons are forcing the patients to opt for the alternative therapies in traditional medicine including Unani system of medicine [5].

Unani physicians have been treating such disorders for many centuries and have mentioned various Unani drugs (single as well as compound) in classical Unani literature for its treatment. While going through the Classical Unani literature, the therapeutic use of a well-known Unani formulation with composition: Katan (*Linum usitatissimum* Linn.), Filfil Siyah (*Piper nigrum* Linn.), and honey with Inkebab of Kalonji (*Nigella sativa* Linn.) in the treatment of Iltehab Tajaweef-e-Anaf Muzmin CRS have been recommended. This oral formulation has been in vogue since ancient times and has proved very effective in upper respiratory tract disorders.

Keeping in mind the complex nature of the disease, low success rate of medical therapy as well as of surgery together with drug resistance, and side effects, need was felt to search an efficient, economic, and safe alternate treatment to resolve this problem.

METHODS

Study design

The present prospective study was carried out in the Department of Moalejat, Faculty of Unani Medicine, Majeedia Hospital, and HAH Hospital, Jamia Hamdard, New Delhi. The study is a randomized, single-blind, and standard controlled trial. The patients of CRS were selected based on the definition of CRS under diagnostic criteria as "Chronic sinusitis is defined as a condition of more than 12 weeks duration that includes two or more major symptoms or at least one major and two or more minor symptoms [6]."

All the patients were enrolled with prior screening as per the protocol approved by the board of studies, Jamia Hamdard. The duration of

the study was 1 year and the duration of the protocol therapy was 6 weeks. The patients were enrolled after positive clinical history and examination with fulfilling both criteria; clinical and radiological. Ethical clearance was taken from the Institutional ethical committee before the enrolling patients for the study.

Test drug

Composition of oral drug

1. Katan (*L. usitatissimum* Linn.) 10.0 g/day
2. Filfil Siyah (*P. nigrum* Linn.) 2.0 g/day
3. Asl-e-Khalis (Honey) 10.0 g/day.

Kalonji (*N. sativa* Linn.) was given as steam inhalation in the test drug group [7].

All the herbs were procured from the local market. The drugs were identified in the Pharmacognosy lab, Department of Botany Jamia Hamdard, New Delhi. The granules dosage form was prepared as per the method prescribed in classical Unani literature.

Control drug

Tablet Alaspan AM (composition): Loratadine 5 mg ambroxol 60 mg Capsule Karvol Plus for inhalation (Indoco Remedies Ltd.).

Dose and administration

Group A (test drug)

The patients were instructed to take oral medication 6.0 g BD after the meal. Kalonji was given to the patients with instruction for pounding than boiling in water and takes inhalation of its medicated steam after covering the head and face with a towel for 10 min BD [8,9].

Group B (control)

The patients were instructed to take Tab Alaspan AM 1 Tab OD and to put Capsule Karvol Plus contents in boiled water and to take its steam inhalation after covering the head and face with a towel for 10 min BD.

Participants

Forty patients who fulfilled the inclusion criteria as given below and consented for participation were taken for study. Guidelines for conducting clinical trials such as Good Clinical Practices and Helsinki declaration of 2013 were adhered to during the study. A detailed history and examination of the patient were recorded in the "Clinical Record File" and patients were screened in the following manner.

Inclusion criteria

Patients with CRS as per the diagnostic criteria between 18 and 70 years age, of both sexes with impaired quality of life, as measured by the Rhinosinusitis Disability Index.

Exclusion criteria

Use of any other investigational agent in the last 30 days, pregnancy and chronic or intermittent use of inhaled, oral, intramuscular, intravenous, and/or potent steroids, diabetes mellitus, chronic renal failure, and hepatic failure [10]. The patients included for the study were taken as withdrawal cases on the basis, that is, failure to follow the protocol, any adverse reaction or adverse event, and drug defaulters.

Time frame

July 2014–June 2015.

Laboratory procedures

Complete blood count with erythrocyte sedimentation rate, blood sugar fasting, and postprandial, immunoglobulin E (0–10=Low, 10–100=Normal, 100 ≥ Elevated) absolute eosinophil count, liver function tests (LFT), kidney function tests (KFT), X-ray chest-posteroanterior view, computed tomography scan paranasal sinuses, nasal swab culture, and sensitivity test and cytology [11], Electro Cardiogram (ECG), Urine R/M [6]. The selected patients were given medication for 1 week at the initial visit followed by biweekly visits and were directed to come for follow-up as per the schedule given in Table 1.

Randomization

All the eligible patients were randomized to two parallel groups; test drug and control group. The statistician generated a randomized list with the help of block randomization method. The assistant assigned the patient to the two groups as per the randomized list. The medical staff and patients were blind to the way of randomization.

Outcome

Assessment of efficacy and safety of test drug was made on the symptomatic improvement after treatment for 6 weeks based on the score of each symptom on visual analog scale. The statistical analysis was done using paired t-test.

RESULTS

Demographic data

The demographic data of 40 patients were recorded at the start of the treatment and analyzed. The Groups A and B were closely matched for age, sex, religion, occupation, socioeconomic status, dietary habits, Mizaj, and symptoms of CRS.

Analysis of demographical data showed no statistically significant difference between the groups at the start of treatment, thus justifying the randomization in both the groups (Table 2).

Safety outcome

The effect on different parameters of LFT (total bilirubin, SGOT, SGPT, and serum alkaline phosphate) and KFT (blood urea, serum creatinine, and serum uric acid) on the patients in the Group A and B did not show any significant statistical difference after the treatment and indicates that the test drugs are safe and did not raise any safety issue.

Effect of treatment on major and minor symptoms of CRS patients

Nasal discharge

In the Group A, the effect was highly significant statistically ($p<0.0001$) as the mean before treatment was 3.55±0.57, after treatment it fell to 0.70±0.92 with a change of 80.28% (Table 3). This may be attributed to the anti-inflammatory effect of Katan because of constituents like fatty acids which have effect on interleukin-6 (IL-6) and 13, cytokines as well as tumor necrosis factor-α [5], Filfil Siyah [12], and Honey as Jazib Ratoobat Fazil [13]. As well as due to mucociliary clearance enhancement effect of *N. sativa* [14].

In Group B, the effect was significant statistically as the mean before treatment was 3.300±0.57, after treatment it was decreased to 1.750±0.91 with a change of 46.96%. This may be attributed to the leukocyte dependent anti-inflammatory and mucolytic effect of

Table 1: Patient's follow-up schedule

Visits	1st	2nd	3rd	4th	5th
Days	0	7th	14th	28th	42th

Table 2: Age and sex data of patients of CRS in test group (A) and control groups (B)

Sex	Study groups		
	Group A	Group B	p-value
Age	Mean±SD 29.7±9.8999	Mean±SD 32.85±10.7521	0.171604 NS at p<0.05
Sex	Mean±SD 1.5±0.219	Mean±SD 1.5±0.219	0 NS at p<0.05

CRS: Chronic rhinosinusitis; NS: Not significant

Table 3: Effect of treatment on major and minor symptoms of CRS patients in test drug and control groups (A and B)

Clinical parameters		Group A				Group B			
		BT	AT	% change	p-value	BT	AT	% change	p-value
Nasal purulence/discharge/discoloration	Mean±SD	3.55 0.51	0.7 0.92	80.28	<0.0001	3.30 0.57	1.75 0.91	46.96	<0.01
Nasal congestion obstruction	Mean±SD	2.95 1.05	0.5 0.09	83.05	<0.0001	2.75 1.16	1.25 1.33	54.54	<0.01
Post-nasal discharge	Mean±SD	2.8 0.70	1.45 0.60	48.21	<0.0001	3.16 0.60	0.21 0.42	93.35	<0.01
Facial pressure/pain	Mean±SD	2.5 1.28	0.5 0.61	80.00	<0.0001	2.60 1.31	1.50 0.83	42.30	<0.01
Facial congestion	Mean±SD	1.650 1.531	0.45 0.51	43.47	<0.0001	2.35 1.53	1.35 0.93	42.55	<0.01
Headache	Mean±SD	1.6 1.43	0.5 0.69	69.13	<0.0037	1.30 1.56	1.15 1.46	11.53	NS
Fatigue	Mean±SD	1.9 1.23	0.5 0.60	73.68	<0.0001	1.60 1.14	1.45 1.15	9.37	NS
Cough	Mean±SD	1.6 1.17	0.2 0.42	87.5	<0.0001	1.95 0.78	0.89 0.32	54.35	<0.01
Sneezing	Mean±SD	1.6 1.32	0.4 0.25	75.00	<0.0003	1.42 1.02	0.72 0.56	49.29	<0.01
Ear fullness	Mean±SD	0.7 1.01	0.1 0.22	85.71	<0.0133	0.42 0.84	0.26 0.56	38.09	<0.48

CRS: Chronic rhinosinusitis, BT: Before treatment, AT: After treatment, NS: Not significant

ambroxol and anti-histaminic effect of loratadine [15] and mucolytic effect of camphor, antibacterial effect of eucalyptus oil [16,17].

Nasal congestion/obstruction

In the Group A, the effect was highly significant statistically (p<0.0001) as the mean before treatment was 2.95±1.05, after treatment it was decreased to 0.50±0.09 with a change of 83.05% (Table 3). This may be attributed to anti-inflammatory effect of Katan [5], Filfil Siyah [12], and honey [18] as well as due to anti-inflammatory and mucociliary clearance enhancement and anti-allergic effect of *N. sativa* [14,19-21]. In Group B, the effect was significant statistically (p<0.01) as the mean before treatment was 2.75±1.16, after treatment it was decreased to 1.25±1.33 with a change of 54.54%.

Post-nasal discharge

In the Group A, the effect was highly significant statistically (p<0.0001) as mean before treatment was 2.80±0.70, after treatment it was reduced to 1.45±0.60 with a change of 48.21% (Table 3). It may be attributed to the astringent effect of Katan after roasting [22,23] and mucociliary clearance enhancement effect of *N. sativa* [14,19-21]. In Group B, the effect was significant statistically (p<0.01) as mean before treatment was 3.16±0.60, after treatment it was reduced to 0.21±0.42 with a change of 93.35% which is due to the anti- histaminic and mucolytic effect of control drug [15-17].

Facial pain/pressure

In Group A, the effect was highly significant statistically (p<0.0001) as the mean before treatment was 2.5±1.28, after treatment it was reduced to 0.5±0.61 with a percentage change of 80% (Table 3). It may be due to analgesic, anti-inflammatory effects of Kalonji [24], Musakkin effect of Filfil Siyah [25-27], and honey [18,28,29]. In the Group B, the effect was significant statistically (p<0. 01) as the mean before treatment was 2.60±1.31, after treatment it was reduced to 1.50±0.83 with a percentage change of 42.30%. This may be due to antihistaminic, mucolytic, and decongestant effects of control drugs [15-17].

Facial congestion

In Group A, the effect was highly significant statistically (p<0.0001) as mean before treatment was 1.650±1.531, after treatment it was reduced to 0.450±0.51 with a percentage change of 43.47% (Table 3). This may be attributed to the anti-inflammatory effect of Katan [5], Filfil Siyah [12], and Jazib Ratoobat Fazil effect of honey [13] and mucociliary clearance effect of *N. sativa* [14]. In Group B, the effect was significant statistically (p<0.01) as mean before treatment was 2.35±1.53, after treatment it was reduced to 1.35±0.93 with a change of 42.55% [15-17].

Headache

In the Group A, the effect was highly significant statistically as the mean before treatment was 1.60±1.43, after treatment it was reduced to 0.50±0.69 with a change of 69.13% (Table 3). This may be due to Musakkin effect of Filfil Siyah [25-27] and Honey [18,28,29]. It may be due to analgesic, ant-inflammatory effects of Kalonji [14,19-21]. In Group B, the effect was not significant statistically (p<0.01) as mean before treatment was 1.30±1.56, after treatment it was reduced to 1.15±1.46 with a change of 11.53%.

Fatigue

In Group A, the effect was highly significant statistically (p<0.0001) as the mean before treatment was 1.9±1.23, after treatment it was reduced to 0.5±0.60 with a change of 73.68% (Table 3). It may be due to immunomodulator and anti-oxidant effect of Kalonji [30,31]. Anti-oxidant effect of Filfil Siyah [32,33] and Katan [34]. In Group B, the effect was not significant statistically as mean before treatment was 1.60±1.14, after treatment it was reduced to 1.45±1.15 with a change of 9.37% (Table 3).

Cough

In Group A, the effect was highly significant statistically (p<0.0001) as the mean before treatment was 1.60±1.17, after treatment it was reduced to 0.20±0.42 with a change of 87.5% (Table 3). It may be due to munaffise balgham [29], Mukhrije balgham effects of Katan, Filfil Siyah, and honey [9,35,36] and anti-histaminic, antibacterial effect of *N. sativa* [14]. In Group B, the effect was significant statistically (p<0.01) as the mean before treatment was 1.95±0.78, after treatment it was reduced to 0.72±0.32 with a change of 54.35%. It is attributed to mucolytic and anti-histaminic effect of control drugs [15-17].

Sneezing

In Group A, the effect was highly significant statistically (p<0.0001) as the mean before treatment was 1.6±1.32, after treatment it was reduced to 0.4±0.25 with a change of 75% (Table 3). It may be due to anti-allergic effect of Kalonji [19,20,21,37]. In Group B, the effect was significant statistically (p<0.01) as the mean before treatment was 1.420±1.02, after treatment it was reduced to 0.720±0.56 with a change of 49.29%. It may be due to anti-histaminic effect of control drugs [15-17].

Ear fullness/ache

In Group A, the effect was highly significant statistically ($p<0.0001$) as the mean before treatment was 0.70±1.01, after treatment it was reduced to 0.1±0.2 with a change of 85.7% (Table 3). It may be due to anti-histaminic, anti-inflammatory effects of Kalonji [24], Musakkin effect of Filfil Siyah [25-27], and honey [18,28,29]. In Group B, the effect was significant statistically ($p<0.01$) as the mean before treatment was 0.42±0.84, after treatment it was reduced to 0.26±0.56 with a change of 38.09%. It may be due to antihistaminic effect of control drugs [15-17].

CONCLUSION

Through all the above parameters of this study, it can be concluded that the test Unani formulation along with Inkebab is considerably safe and well tolerated. It is highly effective to reduce the signs and symptoms of the disease. It may therefore be concluded from the study that the Unani formulation with composition of Katan (*L. usitatissimum* Linn.), Filfil Siyah (*P. nigrum* Linn.), and honey with Inkebab (medicated inhalation) of Kalonji (*N. sativa*) is considerably a promising regime in the treatment of patients with Iltehab Tajweed Anaf Muzmin CRS.

Furthermore, the likely mechanism of the test formulation seems to be due to the anti-histaminic effect of nigellone in *N. sativa* which contains flavonoids which efficiently inhibit production of prostaglandins and leukotrienes from arachidonic acid because they block cyclooxygenase and lipoxygenase and anti-inflammatory constituents like fatty acids of flax seed which has reducing effect on IL-6 and 13, cytokines, as well as tumor necrosis factor-α. Piperine from *P. nigrum* enhances the bioavailability of above mentioned constituents of Katan.

There is a need to carry out a multicentric trial of the test formulation to establish its safety and efficacy of on larger sample size, and for a longer duration and in this way we may provide an efficient, safe, economic and alternate treatment to masses by resolving this problem.

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AUTHORS'CONTRIBUTIONS

Both authors helped me in the preparation of the article by reviewing and editing it.

CONFLICTS OF INTEREST

The authors hereby declare that there are no conflicts of interest.

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