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Evaluation of Therapeutic Efficacy of *Nigella sativa* (Black Seed) for Treatment of Allergic Rhinitis

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1. Introduction

Allergy in general is a common problem in the community, when all aspects of allergy are considered, this condition may well represent the largest single medical problem seen in the United States today and probably in the world.⁽¹⁾ Allergic rhinitis is the commonest allergic disease. It alone is the sixth most prevalent chronic disease in the world, outranking heart disease. ⁽²⁾ There were six factors that stimulated us to choose this disease in our study: firstly, Allergic rhinitis is the commonest allergic disease in the world, affect 10-25% of population ⁽³⁾, secondly, Although it is not a life threatening but from an economic point of view, allergic rhinitis is not a minor problem based on figures reported elsewhere⁽⁴⁾, thirdly, Till now, there is no curative treatment for allergic rhinitis except specific immunotherapy which have many side effects and not suitable for every patient especially when multiple allergens are implicated, which is commonest than single allergen.⁽⁵⁾ fourthly, Serious side effects of pharmacotherapy used in treatment of allergic rhinitis especially steroids which reflected in recent years a trend of increasing use of alternative medicines⁽⁶⁻⁷⁾, fifthly, Allergic rhinitis was frequently trivialized by patients and doctors (particularly non sufferers), this may be because it is not a fatal disease yet it remains a common cause of morbidity, social embarrassment and impaired performance either at school or in the work place, moreover , it may be complicated by a course of other diseases such as sinusitis, otitis media and asthma. ⁽³⁻⁸⁾ and lastly, in a previous studies, it has been proved that *Nigella sativa* is an effective treatment of asthma. It also showed an improvement in the associated nasal symptoms that accompanied asthma ^(9,10) Administration of black seed oil significantly reduced the level of allergen induced lung remodeling ⁽¹¹⁾.

Allergic rhinitis is a common disease, accounting for at least 2.5% of all physician visits, 2 million lost school days per year, 6 million lost work days, and 28 million restricted work days per year. At least \$ 5.3 billion is spent annually on prescription and over-the-counters medications for allergy⁽¹²⁾ . Between 10 and 25% of the population is affected⁽³⁾ and the prevalence in urban areas is increasing .The prevalence is lowest in children below age 5 , rises to a peak in early adulthood and declines thereafter. The 4 year remission rate reported to be 10% in males and 5% in females.⁽¹³⁾

N.S. is an annual famous herb, the respect of which in the medical field is taken from a religious origin when the prophet Mohammed ρ advised people to use it in order to treat different diseases. The seeds of N.S are considered as carminative, stimulant, galactoguge, anti tussive, anti flu and anti flatulence e.t.c. (2). Anti allergic effects of N.S. was reported (2). The active ingredient is thymoquinone with its carbonyl polymer. (14) Recently reported study suggest the N. sativa could reduce the presence of the nasal mucosal congestion, nasal itching, runny nose, sneezing attacks, turbinate hypertrophy, and mucosal pallor during the first 2 weeks(15). Furthermore, N. sativa supplementation during specific immunotherapy of AR may be considered a potential adjuvant therapy (16) and it was equal therapeutic activity in relieving the symptoms of seasonal AR to cetirizine, without its side effects (17).

1.1 Aim of the study

To evaluate the therapeutic effect of systemic forms of black seed oil in allergic rhinitis

2. Materials and methods

2.1 Study population

A total of 188 patients with allergic rhinitis symptoms of different severities (mild, moderate and severe) with age ranging from 6-45 years, were included in this study [Table 1]. This double blinded clinical trial was performed during the period between January 2009 to June 2010 in the out-patient clinic of centre of allergy in Tikrit Teaching Hospital (TTH) in Salahudean governorate, Iraq. The patients were either referred from medical or ENT departments, from the out patients in the same hospital and those who attended the allergy centre to have immunotherapy.

2.2 Diagnosis of asthma and allergic rhinitis

The diagnosis of asthma and classification was performed by specialist physicians based on the National Heart Blood and Lung Institute / World Health Organization (NHLBI/WHO) workshop on the Global Strategy for Asthma (18). Allergic rhinitis diagnosis was performed according to previously reported guidelines (19).

2.3 Skin prick test

The skin prick tests were performed for all patients and control and evaluated in accordance with European Academy of Allergy and Clinical Immunology subcommittee on allergy standardization and skin tests using standards allergen panel (Stallergen, France). The panel for skin test include: dust mite (Dermatophagoides farina, Dermatophagoides pteronyssinus), Aleternaria, Cladosprium, Penicillum mixture, Aspergillus mixture, Grasses mixture, Feather mixture, Dog hair, Horse hair, Cat fur, Fagaceae, Oleaceae, Betulaceae, Plantain, Bermuda grass, Chenopodium and Mugwort. All tests were performed in the outpatient Asthma and Allergy Centre, Mosul by a physician using a commercial allergen extracts (Stallergen, France) and a lancet skin prick test device. A wheal diameter of 3 mm or more in excess of the negative control was considered as positive test result.

2.3.1 Allergen extracts for skin prick test

Therapeutic vaccines containing allergen extracts were purchased from Stallergen, France. Both aqueous and glycerated extracts were used to achieve a concentrate of 1:100 w/v of

the mixed extract. In standardized extracts the stock formulation was prepared by tenfold dilution. Separate vial was used for allergen extract to reduce proteolysis degradation. All extracts were stored at 8 °C . Therapeutic vaccine varied with each individual patient based on specific allergen identified during testing. Moist patients received a variety of aeroallergen combination.

Variable	Active group	Control group	Total Number [%]
Patients total number	115	95	210
Patients completed study	102	86	188
Female/Male	58/44	48/38	106/82
Mild group			
Total number	35	30	65
Patient completed study	31	27	58
Female/Male	18/13	16/11	34/24
Moderate group			
Total number	50	40	90
Patient completed study	44	37	81
Female/Male	25/19	20/17	45/36
Severe group			
Total number	30	25	55
Patient completed study	27	22	49
Female/Male	15/12	12/10	27/22
Gender			
Male			82 [43.6]
Female			106 [56.4]
Age in year			
6 -15			60 [31.9]
16-25			75 [39.8]
26-35			36 [19.1]
36-45			17 [9.0]
Duration in year			
Mild			1-4
Moderate			2-7
Severe			2.5-11
Skin test			
Single			63 [33.5]
Multiple			125 [66.5]
Two			76 [40.4]
Three			40 [21.3]
Four			9 [4.8]
HDM			103 [54.7]
Candida			70 [37.2]
Molds			65 [34.5]
Grass mixture			58 [30.8]
Animal dander			32 [17.0]
Other pollen			43 [22.8]
Associated diseases			
Conjunctivitis	68 [66.6]	43 [50]	111 [59]
Asthma	33 [32.3]	26 [30.2]	59 [31.4]
Sinusitis	15 [14.7]	17 [19.7]	32 [17]
Urticaria	12 [11.7]	5 [5.8]	17 [9]
Otitis media	4 [3.9]	3 [3.4]	7 [3.7]
Polyps	4 [3.9]	2 [2.3]	6 [3.2]

Variable	Active group	Control group	Total Number [%]
Exacerbating factor			
Allergen exposure	89 [87.2]	64 [74.2]	153 [81.4]
URT infection	39 [38.2]	24 [27.9]	63 [33.5]
Temperature change	26 [25.4]	22 [25.5]	48 [25.5]
Smoke & irritants	21 [20.5]	14 [16.2]	35 [18.6]
Hormonal	4 [3.9]	2 [2.3]	6 [3.2]
Severity			
Mild	31 [30.4]	27 [31.4]	58 [30.8]
Moderate	44 [43.1]	37 [43.0]	81 [43.1]
Severe	27 [26.5]	22 [25.6]	49 [26.1]
Pattern			
Seasonal	41 [40.2]	37 [43.0]	78 [41.5]
Mild	11 [26.8]	9 [24.3]	20 [25.6]
Moderate	20 [48.8]	20 [54.1]	40 [51.3]
Severe	10 [24.4]	8 [21.6]	18 [23.1]
Perennial	61 [59.8]	49 [57.0]	110 [58.5]
Mild	20 [32.8]	18 [36.7]	38 [34.5]
Moderate	24 [34.3]	17 [34.7]	41 [37.3]
Severe	17 [27.9]	14 [28.6]	31 [28.2]
Family atopy			
Mild			
Atopic	11 [35.5]	13 [48.1]	24 [41.3]
Non-atopic	20 [64.5]	14 [51.9]	34 [58.7]
Moderate			
Atopic	21 [47.7]	19 [51.4]	40 [49.3]
Non-atopic	23 [52.3]	18 [48.6]	41 [50.7]
Severe			
Atopic	17 [63]	14 [63.6]	31 [63.2]
Non-atopic	10 [37]	8 [36.4]	18 [36.8]
IgE IU/ml			
Mild	143	168	
Moderate	176	188	
Severe	393	361	

Table 1. Patients characteristics at time of enrolled in the trial.

2.4 Determination of total serum IgE

ELISA was performed to estimate the total serum IgE level as a serological marker for treatment response monitoring.⁽²⁰⁾ Total serum IgE was determined by enzyme linked immunosorbant assay kit (Biomaghreb). Results were interpreted as allergy not probable if serum IgE was lower than 20 IU/ml, allergy is possible if IgE value is between 20 and 120 IU/ml and allergy is very probable if IgE is more than 120 IU/ml.

2.5 Classification of patients

In classifying the patients, two types of classification were adopted^(3,5)

According to severity of symptoms. They were also sub classified into the following: mild group :A total 58 patients (31 active and 27 control); Moderate group: A total 81 patients (44 active and 37 control); and Severe group: A total 49 patients (27 active and 22 control)

According to allergens. The patients were sub classified into the following :

- Seasonal class: A total 78 patients (41 active and 37 control).
- Perennial class: A total 110 patients (61 active and 49 control).

2.6 Family history of allergy

Because allergic diseases are familial diseases, some emphasis was laid on the families of patients to know the percentage of them that had allergic diathesis.

3. Systemic use of the black seed oil

The herb was given in the form of capsules, one capsule three times a day .Each capsule was about 0.6-0.8 gm of oil (which is about half of the dose that used in asthma in a previous study)⁽⁹⁾ The control group received same shaped capsules but they contained ordinary food oil. The treatment was given for 6 weeks for both groups . The results were recorded on the patient's questionnaire each visit .The same routine physical examination and laboratory investigations as mentioned earlier were done and recorded in addition to the clinical evaluation which was done according to the following criteria:

3.1 Clinical assessment (symptom score)

During each visit, the patient was examined clinically for vital signs and questioned about the improvement in his day and night symptoms (Rhinorrhoea, nasal obstruction, paroxysm of sneezing, night snoring, daily physical activities, school attendance and affection of life quality). Symptom score was of 4 points scale (0-3) according to the classification of rhinitis symptoms as specified by:

0. No symptoms.

1. Mild symptoms: Symptoms not interfere with sleep, normal daily activities, (sports, leisure), no trouble of some symptoms, sneezing (not more than 3 in each attack or paroxysm), with mild runny nose (of no more than 1hour).^(3,5)
2. Moderate symptoms: Are of one or more items of the following: abnormal sleep, impairment of daily activities, (sports, and leisure), problems caused at work, at school with troublesome symptoms: longer attack > 1h. -<8 with uncomfortable stuffy, runny nose, sneering 4-10 sneeze each attack. ^(3,5)
3. Severe symptoms: The same as moderate but more severe, more nasal blockage and sleep interference with severe distressing stuffy, runny nose for more than 8h. attack with sneeze more than 10 times each paroxysm. ^(3,5)

3.2 Tolerability to the exacerbating factors

Many precipitating factors such as aeroallergen exposure, cold exposure, infection (sinusitis), drugs ...etc. may precipitate the condition, so the response to the exacerbating factors were assessed in each visit by skin test.

3.3 Other associated allergic diseases

Other allergic diseases such as asthma, conjunctivitis and urticaria were also recorded in each visits.

3.4 Side effects

Side effects that were shown by the patients were recorded for both systemic and nasal uses.

3.5 Statistical analysis

CHI square analytic system (X^2) with Yates correction was used to compare between active and placebo groups. However, Chi Square is calculated only if the expected cell frequencies

are equal to or greater than 5. While Fisher Exact Probability Test is used if some cells are less than five. Student t test is used to determine the significance of IgE differences between the groups.

4. Results

For systemic trial, a total of 210 patients were included in the study. Of them 115 patients received the treatment [active group] and 95 patients were the controls. The patients were divided according to their disease severity, and each of the above groups was subdivided into active and control groups. As mentioned earlier, 188 patients completed the course of treatment in this study while 22 patients withdrawn from the study [Table 1].

4.1 Age and sex frequency distribution

The eligible patients for analysis were subdivided into 3 groups as follow:

Mild group: A total of 58 patients were included, of them: 31 patients (18 female and 13 male) were mild active group and 27 patients (16 female and 11 male) were mild control group. Mild group patients accounts for 30.8% of the total .

Moderate group: A total of 81 patients were included , of them : 44 patients (25 female and 19 male) were moderate active group and 37 patients (20 female and 17 male) were moderate control group. Moderate group patients accounts for 43. 1% of the total.

Severe group: A total of 49 patients were included, of them: 27 patients (15 female and 12 male) constitute the severe active group while 22 patients (12 female, and 10 male) constitute the severe control group. Severe group patients accounts for 26.1% of the total. Male patients account for 43.6% and female ones account for 56.4% of total patients. The highest frequency of AR is in the age group of 16 -25 years and then the declines with age.

Frequency distribution of the patients according to the duration of AR : Severe group had the longest duration of the diseases which was from 2.5 years-11 years, while mild group had the shortest duration range which was from 1 years- 4 years.

Classification of the patients according to allergen's type:

One of the important classification of the allergic rhinitis depending on the type of exacerbating allergen into the seasonal and perennial type. Perennial type (110 patient, 58.5%) was more common than seasonal type (78 patient, 41.5%).

4.2 Monthly distribution of the patients

The monthly distribution of the patients indicated that 63.2% of cases were reported in March, April and May.

4.3 Exacerbating factors

The potent exacerbating factor in both groups was allergen exposure which account for 87.2% ,(89 patients) in active group and 74.2% (64 patients) in control group. The upper respiratory tract infection forms 38.2% ,(39 patients) in active group and 27.9% ,(24 patients) in control group. This is followed by temperature and humidity changes with cold exposure which was 25.4%,(26 patients) in active group and 25.5% ,(22 patients) in control group. Then smoke and irritants factor which was about 20.5% ,(21 patients) in active group and 16.2%,(14 patients) in control group .The last exacerbating factor that affect the disease in the

studied patients was hormonal factor (i.e. pregnancy) which was 3.9% ,(4 patients) in active group and 2.3% ,(2 patients) in control group.

4.4 Family atopic diathesis

As it is clear from the history of patients as shown in Table 3: atopic family diathesis with positive family history of allergy (in any form of allergy as asthma, eczema, and allergic rhinitis) was found in 41.3% (24 patients) of total mild group (13 control and 11 active) .This increased to 49.3% (40 patients) of total moderate group (19 control and 21active) .While the highest incidence was in severe allergic rhinitis group which was 63.2% (31 patients) (14 control and 17 active) .This means that the disease is generally more severe in patients of atopic diathesis or tendency.

4.5 Associated diseases

Conjunctivitis was the most common associated disease which accounted for 66.6% (68 patients) of total active group and 50% (43 patients) of total control group. Asthma was the second common associated disease. In active group it is accounted for 32.3% (33 patients) and in control group it is 30.2 (26 patients) while sinusitis which comes thirdly, accounted for 14.7% (15 patients) of active group and 19.7% (17 patients) of control group. The lowest associated disease was nasal polyposis which account for 3.9% (4 patients) of total active group and 2.3% (2 patients) of total control group.

4.6 Skin test results

In 33.5% of patients (63 patients) the test was positive to only one allergen and in 66.5% (125 patients) was positive to multiple allergen. Double allergen positive skin test results form 40.4% (76 patients), while triple allergen positive skin test results form 21.3% (40 patients) and lastly quadrant allergen positive skin test results form 4.8% (9 patients) of total 188 patients. For frequency distribution of the skin tests result according to allergens type, the highest incidence was HDM which accounted for 54.7% (103 patients), then *Candida albicans* 37.2% (70 patients). Animal dander account for 17% (32 patients), forms the lowest frequency.

4.7 IgE serum level

Serum IgE mean was 143 IU/ml in mild active and 168 IU/ml in mild control groups and were lower than those of the moderate groups (active,176 IU/ml; control, 188 IU/ml). This in turn was less than that of severe allergic rhinitis of both active (393 IU/ml) and control (361 IU/ml) groups.

4.8 Effects after 6 weeks systemic treatment

4.8.1 Symptomatic response: [Table 2]

Mild group response: In mild active group,19 patients out of 31,(61.3%), became free from symptoms after a three week of treatment with black seed oil .This percentage is considered highly significant ($P=0.000$) when it is compared with mild control group of which only 4 patients out of 27 (14.8%) , became free from symptoms. After six weeks of treatment, the results of mild group are as following : 30 patients (96.7%) did not show symptoms .This results is highly significant ($P=0.000$) when it is compared with mild control group of which only 7 patients (25. 9%) did not show symptoms.

Group		Active group				Control group			
		0W	3W	6W	P value	0W	3W	6W	P value
Mild	Symptomatic	31	12	1		27	23	20	
		(100%)	(38.7%)	(3.2%)		(100%)	(85.1%)	(74.5)	
	Symptom free	0	19	30	0.000	0	4	7	NS
		(0%)	(61.3%)	(96.7%)		(0%)	(14.8%)	(25.9%)	
Moderate	Symptomatic	44	21	9		37	32	29	
		(100%)	(47.7%)	(20.4%)		(100%)	(86.4%)	(78.3%)	
	Improved	0	17	21		0	5	6	
		(0%)	(38.6%)	(47.7%)		(0%)	(13.5%)	(16.20%)	
	Symptom free	0	6	14	0.000	0	0	2	NS
		(0%)	(13.6%)	(31.8%)		(0%)	(0%)	(5.4%)	
Severe	Symptomatic	27	17	11		22	19	17	
		(100%)	(62.9%)	(40.7%)		(100%)	(86.3%)	(77.2%)	
	Improved	0	8	10		0	3	5	
		(0%)	(29.9%)	(37%)		(0%)	(13.6%)	(22.7%)	
	Symptom free	0	2	6	NS	0	0	0	NS
		(0%)	(7.4%)	(22.2%)		(0%)	(0%)	(0%)	

Table 2. Symptomatic response at 6 weeks systemic use

Moderate group response: In moderate group, after 3 weeks of treatment, 17 patients out of 44 (38.6%) demonstrate partial improvement while 6 patients (13.6%) became symptoms free patients. So 23 patients out of 44 (52.2%) demonstrated either partial or total improvement of their signs and symptoms. These results are highly significant ($P=0.004$) as compared with moderate control group from whom only 5 patients out of 37 (13.5%) got partial improvement at the end of 3 weeks. At the end of 6 weeks treatment in moderate active group; 21 patients (47.7%) show partial improvement and 14 patients (31.8%) were symptoms free. Thus, the total improved patients of moderate active group at the end of 6 weeks (partially and a totally improved) were 35 patients out of 44, nearly about 79.5%. This is significant with ($P=0.02$) as compared with moderate control group at 6 weeks treatment of which 6 patients (16.2%) got partial improvement while only 2 patients (5.4%) got no symptoms. Therefore in moderate control group 8 patients (12.5%) improved (partially, and totally) at the end of the 6 weeks.

Severe group responses: For severe active group, 8 patient out of 27 (29.9%) show partial improvement while 2 patients (7.4%) became free from symptoms after 3 weeks treatment with black seed capsules. This indicate that 10 patients (36.3%) demonstrate treatment benefit (partially or totally). While in severe control group, 3 patients out of 22 (13.6%) got partial improvement after 3 weeks of treatment with ordinary food oil capsules and none became non

symptomatic. At the end of 6 weeks of treatment for severe active group: 10 patients (37%) were got partial improvement while 6 (22.2%) got symptoms free. Thus collectively improved patients were 16 patients (59.2%). Clinically, this is considered a good result and is statistically significant ($P=0.026$) as compared with the results of severe control group were only 5 patients (22.7%) got partial improvement. The differences in clinical improvement between 3 and 6 weeks treatment duration was highly significant ($P=0.000$) as compared to baseline for both mild and moderate active group. However, it was not significant in case of severe group.

4.9 Serum IgE

The mean serum IgE level in mild active group decreased from 143 IU/ml at the baseline estimation to 91 after a 6 week treatment with *N. sativa* oil, while in mild control group, it decreased from 168 IU/ml to 131 IU/ml after a 6 week treatment with ordinary food oil. In moderate active group, it decreased from 176 IU/ml at the baseline estimation to 127 IU/ml after 6 weeks of treatment while for moderate control group also there was reduction in the IgE average level from 188 IU/ml to 152 IU/ml. In severe group, the IgE average level of severe active group decreased from 393 IU/ml to 354 IU/ml and the same thing occurred in control group which decreased from 361 IU/ml at the baseline estimation to 335 IU/ml at the end of the 6 week treatment. The reduction in serum IgE means level pre- and post-treatment was significant for both active and control groups, however, there was a significant differences between active and control groups [Table 3].

		Mean IgE IU/ml [SD]		
		Mild	Moderate	Severe
Active	Pretreatment	143 [8.9]	176 [11.3]	393 [18.7]
	Post treatment	91 [7.1]	127 [7.7]	354 [12.3]
	Difference	52	49	39
	P value	0.000	0.000	0.000
Control	Pretreatment	168 [9.6]	188 [10.1]	361 [16.4]
	Post treatment	131 [10.4]	152 [12.5]	335 [17.5]
	Difference	37	36	26
	P value	0.000	0.000	0.000
P value for difference between active & control		0.000	0.000	0.007

Table 3. Effect of systemic treatment with *N. sativa* on IgE [IU/ ml] serum level.

4.10 Tolerability to the exacerbating factors

Improvement in tolerability of the exacerbating factors in total active group and total control group are shown in Table 6. The response to allergen exposure has improved from 24.5% after 3 weeks ($P=0.001$) treatment to 37.5% at 6 weeks ($P=0.000$) treatment in the active group while in control group, the improvement was much less. The allergen exposure tolerability was significant during the treatment course ($P=0.000$), however, there was no significant difference between 3 and 6 weeks of treatment period. The response to temperature variation has also improved to about 7.8% at the end of 3 weeks ($P=0.01$) and to about 11.7% at the end of 6 weeks treatment in active group ($P=0.001$). This is better than that of control group which was about 2.3 at the end of 3 weeks and increased to 4.6 (4 patients) at the end of 6 weeks. Another environmental factor that showed improvement

was exposure to irritant gases which increased from 5.8% at the 3 week ($P=0.03$) treatment in active group to 9.8% at the end of 6 weeks ($P=0.003$) while in control group, a minor improvement occurred, which was from 2.31 after 3 weeks of treatment to 3.4% after 6 weeks of treatment. [Table 4].

Variable	Active groupNumber [%]	Control groupNumber [%]	P value
Allergen exposure			
3 week	25 [24.5]	3 [3.4]	0.000
6 week	38 [37.2]	5 [5.8]	0.000
P value 0,3 & 6 weeks	0.000	NS	
0 & 3 weeks	0.001	NS	
0 & 6 weeks	0.000	NS	
3 & 6 weeks	NS	NS	
Temperature change			
3 week	8 [7.8]	2 [2.3]	NS
6 week	[11.7]	2 [2.3]	0.02
P value 0,3 & 6 weeks	NS	NS	
0 & 3 weeks	0.01	NS	
0 & 6 weeks	0.001	NS	
3 & 6 weeks	NS	NS	
Irritant exposure			
3 week	6 [5.8]	4 [4.6]	NS
6 week	10 [9.8]	3 [3.4]	NS
P value 0,3 & 6 weeks	NS	NS	
0 & 3 weeks	0.03	NS	
0 & 6 weeks	0.003	NS	
3 & 6 weeks	NS	NS	

Table 4. Tolerability to the exacerbating factors

4.11 Symptomatic response in associated allergic illnesses

The common associated allergic disease allergic rhinitis was allergic conjunctivitis which accounts for 66.6% (68 patients) and this was decreased to 21.5% (22 patients) at the 3 weeks ($P=0.000$) treatment then became 17.6% (18 patients) at the end of 6 weeks ($P=0.000$) treatment. While in control group, conjunctivitis affect 50% (43 patients) which showed some improvement after 3 weeks to 44.1% (38 patients) and decreased lastly to 39.5% (34 patients) at the end of 6 weeks treatment. The differences between active and control groups was significant for both 3 and 6 weeks course treatment ($P=0.001$). Table 5.

Asthma which was presented in 32.3% (33 patients) of active group decreased to 21.5% (22 patients) after 3 weeks and then decreased to 18.6% (19 patients) at end of 6 weeks while in control group, 30.2% (26 patients) have asthma which showed improvement by decreasing in symptomatic patients to 26.7% (23 patients) at 3 weeks treatment, then decreasing to 24.4% (21 patients) at the end of 6 weeks treatment. However, the differences between active and control groups was not significant. Table 5.

The last associated disease was urticaria which showed some improvement: 9.8% (10 patients) were had symptoms at the beginning of the study and decreased to 6.8% (7 patients) at 3 weeks treatment which then decreased to 4.9% (5 patients) at the end of 6 weeks. While in control group, 8.1% (7 patients) have symptomatic urticaria decreased to 6.9% (6 patients) by 3 weeks and remained the same at the end of 6 weeks treatment. The demonstrated differences between active and control groups was not significant. Table 5.

Variable	Active group Number [%]	Control group Number [%]	P value
Conjunctivitis			
0 week	68 [66.6]	43 [50]	0.03
3 week	22 [21.5]	38 [44.1]	0.001
6 week	18 [17.6]	34 [39.5]	0.001
P value 0,3 & 6 weeks	0.000	NS	
0 & 3 weeks	0.000	NS	
0 & 6 weeks	0.000	NS	
3 & 6 weeks	NS	NS	
Asthma			
0 week	33 [32.3]	26 [30.2]	NS
3 week	22 [21.5]	23 [26.7]	NS
6 week	19 [18.6]	21 [24.4]	NS
P value 0,3 & 6 weeks	NS	NS	
0 & 3 weeks	NS	NS	
0 & 6 weeks	0.03	NS	
3 & 6 weeks	NS	NS	
Urticaria			
0 week	10 [9.8]	7 [8.1]	NS
3 week	7 [6.8]	6 [6.9]	NS
6 week	5 [4.9]	6 [6.9]	NS
P value 0,3 & 6 weeks	NS	NS	
0 & 3 weeks	NS	NS	
0 & 6 weeks	NS	NS	
3 & 6 weeks	NS	NS	

Table 5. Symptomatic response in associated allergic illness.

Group	Sub group	Improved patients on 3 and 6 weeks		Withdrawal effect on improved patients	
		3 weeks	6 week	Patients with recurrence of symptoms	Not symptomatic Patients
Mild AR group (58)	Active group 31	19 61.3%	30 96.7%	25 80.6%	5 16.1%
	Control group 27	4 14.8%	7 25.9%	2 7.4%	5 18.5%
	P value			0.000	
Moderate AR group(81)	Active group 44	23 52.2%	35 79.5%	32 72.7%	3 6.8%
	Control group 37	5 13.5%	8 21.6%	3 8.1%	5 13.5%
	P value			0.009	
Severe AR group (49)	Active group 27	10 37.3%	16 59.2%	14 55.5%	2 7.4
	Control group 22	3 13.6%	5 22.7%	2 9%	3 13.6%
	P value			NS	

Table 6. Two weeks systemic oil treatment with drawl effect

4.12 Factors associated with poor response to systemic NS treatment in AR

The following factors seem to be associated with poor response to the systemic herb treatment [Table. 6]: Multiple allergic diseases in the same patients, High IgE serum level, Gender (female), Perennial type more than seasonal one, Atopic diathesis, and Older age group.

4.13 Two weeks systemic oil treatment withdrawal effect

Two weeks systemic oil treatment with drawl effect is shown in Table 9. In mild active group, from 96.7% that improved at 6 weeks treatment with black seed oil, 80.6% had recurrence of their symptoms which was significant ($P=0.000$) when compared with mild control group. The same pattern reported for moderate group in which, from 79.5% improved at the end of 6 weeks NS oil treatment, 72.7% had recurrence of their symptoms which was significant ($P=0.009$) as compared to control group. Severe group also showed no significant difference in recurrence rate.

4.14 Side effects

The side effect of systemic NS treatment was diarrhea (10.7%) and nasal dryness (0.9%).

5. Discussion

Allergic rhinitis represents a global health problem. It is a common disease worldwide by which at least 10-25% of the population is affected and its prevalence is increasing. Although allergic rhinitis is not usually a severe disease but it alters the social life of patients and affect school performance and work productivity, and so, the costs incurred by rhinitis are substantial. (2) New knowledge about the mechanisms underlying allergic inflammation of the air ways has resulted to better therapeutic strategies, like immunotherapy with engineered allergen. Even trails of laser surgery for treatment of AR by laser turbinectomy (Tiny biopsy specimens) with local destructive effect of laser energy on the glandular acini and on the surrounding cholinergic nerve fibers which leads to decrease nasal secretions.(21). But still pharmacotherapy is the corner stone in the management of this illness, followed by immunotherapy(22). All these therapeutic strategies have many side effects, some of them may prove dangerous or even lethal, and in addition, there is no curative therapy.

One of the good substitutions is the use of herbal medicine and one of the ancient herbs that was used medically for many diseases was black seed extract(23). This herb has been used for many diseases since no signs of toxicity or serious side effects were known in antiquity (24). The role of herbal medicine in allergic rhinitis as an effective therapy has not been studied extensively (15,16,17,25) and up to our knowledge, the use of topical N.S extract in treating A.R has not been studied yet. Although few studies have been conducted to illustrate the possibility of therapeutic effect of this herb on other allergic diseases like asthma(9,2,10,11,26) and allergic disease of the skin like urticaria(27).

Females were affected more than males. This may be due to the fact that most of our patients came from rural areas where females used to work long hours in the fields. Other studies showed no sex difference or slight male predominance (8) . About 71.7% of the patients were less than 25 years old which means that the onset mainly started during the childhood and adolescence. This goes in line with other studies (28) because allergy is a less common cause of rhinitis in elderly as compared with other forms of rhinitis like atrophic rhinitis (3) . The disease duration has a big correlation with the severity of the disease since

the shortest duration was of mild type and the longest duration was of the severe allergic rhinitis group. This may be due to the fact that chronicity of the disease leads to more allergen exposure which, in turn, leads to more non specific hyper reactivity. Non specific nasal hyper reactivity is an important feature of chronic allergic rhinitis and it is defined as: increase nasal response to a normal stimuli resulting in sneezing, nasal congestion and/or secretion^(3,8) which lastly leads to more severe and chronic disease.

Perennial type rhinitis were more than seasonal type. This may be due to more exposure since perennial allergens are present every were and at any time. The peak incidence occurred in spring season (from March to May with highest level in the April). This is due to the peak time for tree pollinosis in this area happens during these months which include exacerbation of seasonal type AR as well as perennial type . These results contradicts with the results of some other studies which were done in different geographical areas with different ecological environments ⁽²⁹⁾ .

The highest aggravating factor was allergen exposure simply because of the agricultural nature of the areas with more pollinosis and dampness, then upper respiratory tract infection followed by temperature changes then irritants and lastly hormonal factor. AR has mainly a bad course in the pregnant women since nasal obstruction may be aggravated by the pregnancy itself. ^(3,5) Allergic disease mainly worsened during pregnancy. This is proved by the following physiological and epidemiological observations⁽⁵⁾ :

The major physiologic factors are the direct and indirect effects of pregnancy associated hormones on nasal mucosa, that is estrogen cause nasal mucosal swelling, possibly through stimulation of local Ach production⁽⁵⁾.

- Cyclic changes in human female nasal mucus are characterized by the formation of large ferns during ovulation followed by their disappearance premenstrual. ⁽⁵⁾
- Recent ultrastructural and histochemical studies have revealed the increased activity of nasal mucous glands during pregnancy. A change similar to that is found in estrogens and progesterone contraceptive users. ⁽⁵⁾
- Pregnancy associated hormones may indirectly affect the nose through their circulatory effect. The increased circulating blood volume during pregnancy combined with nasal vascular smooth muscle relaxation for progesterone may contribute to the nasal mucosal congestion that occurs frequently during pregnancy. Epidemiologic observations showed that allergic rhinitis may occur in up to 20% of the population of women of child bearing age. ⁽⁵⁾

It has been noticed that patients with AR have a strong family history of allergic disease. This finding is in accordance with well documented fact in allergic disease. ⁽³⁰⁻³²⁾ the commonest associated illnesses was allergic conjunctivitis which may be as an entity associated with allergic rhinitis due to the same mechanism with the same allergen. Yet, it may be a reflex of histamine granules degranulation and it is considered one of allergic rhinitis co-morbidities.⁽³⁾ Allergic asthma comes secondly in associated disease's frequency suggesting the concept that say "one air way, one disease". ⁽³³⁾ Sinusitis is also one of the associated diseases and contributors to allergic rhinitis.^(8,34)

The commonest allergen implicated is house dust mite (HDM) which may be the worldwide commonest cause of allergic rhinitis.⁽³⁵⁾ One example to the importance of (HDM) in respiratory allergens is that the incidence of the atopy in southern France is 30% but the prevalence of allergic asthma and rhinitis is greater in the low land compared to the ALPS. The reason for this difference in the prevalence of allergies (in the same population type and

country) is considered to be the lower HDM population found above 1500 meters, and inhalant allergic patients are cleared an Alpine holiday despite the cold weather and exercise.⁽³⁶⁾ The severe symptoms patients had higher total serum IgE level than moderate symptomatic patient which in turn had higher level than mild symptomatic one. From this we can conclude that then increased in total serum IgE level correlates with the severity of the diseases.

The mild and moderate active groups patients showed excellent improvement in clinical symptoms at the 3 and 6 week extract treatment which is statistically a highly significant as compared with control groups. The severe group also showed a good improvement in clinical symptoms for active group but was not statistically significant for 3 weeks treatment course. However, the treatment effect was statistically significant after 6 weeks course of therapy with black seed oil. The response to treatment in the severe group was lower than that in mild and moderate groups and this may be due to more associated co-morbidities especially asthma which may need higher doses of N.S. The improvement effect that is seen in different groups may be related to the antihistaminic activity of nigellon through membrane stabilizing action⁽³⁷⁾, Anticholinergic activity by competitive property of the pinene⁽²⁷⁾, Anti inflammatory effect of thymoquinone by effect on cyclo oxygenase & lipo oxygenase pathways^(29,38), immunomodulatory activity, and antioxidant activity.⁽²³⁾

The results also showed that the seasonal type has better responses than the perennial type which may be due to less nasal hyper reactivity appears because of less exposure to allergens (seasonal exposure only which don't continue very long) and decrease in the level of pollination may occur through this 6 weeks treatment leads to decrease the triggering factor which result in the decrease of allergic reaction associated with the stabilizing action of *N. sativa* extract which leads to better response and an improved clinical state.

Males patients show better treatment responses. This may be due to that males had less allergen exposure because of agricultural nature of this area which depends on females and hormonal changes in female through menstrual cycle changes affect the nasal mucosa and enhance disease exacerbations.

IgE level estimation by ELISA showed no switching of any patients from probable allergic group to non allergic group with increased level in some patients even after taking *N. sativa* extract for 6 weeks. The average of each group patients showed some decline in their level than that of the baseline estimation but this reduction was significant for active and control groups. However, the reduction in serum IgE following 6 weeks of black seed treatment was higher as compared to control group.

Salem⁽³⁹⁾, reported that administration of nigellone to children and adults during the treatment of asthma, decreased the IgE level and eosinophil count. The reduction in total serum IgE level in control group may be a reflection of reduction in allergen exposure. The patients improved clinically without reduction in total serum IgE level to the level of non allergic individuals was due; firstly, measurement of total serum IgE level is not a measure of a specific IgE Ab which more specific predictor of atopy⁽²⁸⁾. Secondly, since mast cell-bound and non circulating IgE Ab are functionally important in initiating atopic reaction upon exposure to allergen. Measurement of the total quantity of IgE fixed to high affinity mast cell and basophile receptors (FC_εR₁) might be more relevant to atopy than serum circulating IgE Ab but since there is no technique for making such measurement currently, there is only an estimation of skin mast cell-bound IgE by thresholds dilution skin testing

with heterologous anti-IgE that show the tissue IgE level is much higher in atopic individuals than the normal population. (28)

Improvement in tolerability to the exacerbating factors in active group, as it is compared with the control group after systemic treatment, may be due to the stabilizing effect of N.S on mast cell granules and antihistaminic properties of nigellone thymoquinone and subsequently prevent histamine release from macrophages, intracellular calcium release, protein kinase C activation and oxidative energy metabolism (40). In a recent study, addition of NS seed to immunotherapy significantly increase the phagocytic and intracellular killing activities of PMNs in patients with AR (16). Furthermore, NS inhibits the COX and 5-lipoxygenase pathways of arachidonic acid metabolism and decrease the synthesis of thromboxane and leukotrienes (23, 41, 42). Since leukotrienes are a potent mediators that play a major role in allergic diseases including allergic rhinitis and histamine plays an important role in immediate hypersensitivity reactions, thus the above findings may explain the mechanism mediating the efficacy of NS in allergic diseases (2,16).

Improvement in associated allergic symptoms of conjunctivitis, asthma, and urticaria in active groups was more than that of control groups revealed clearly the multiple anti allergic actions of *N. sativa* extract. This may be due to augmentation of PMN function induced by *N. sativa* seed oil (16, 39), antihistaminic activity (40), antioxidant activity (43), inhibition of prostaglandin production (44) and antiinflammatory activity (45).

Factors associated with poor response to systemic NS treatment include: a) Multiple allergic disorders which may need more dose because the multiple allergic disease especially asthma are more complicated in mechanism than allergic rhinitis and the patients usually have bronchial hyper reactivity. The main antihistaminic action which act on AR occur at the lower doses of *N. sativa*.(37) While anti-inflammatory action to treat asthma needs higher doses for longer period.(27,38) . b) High IgE level which reflects allergen exposure and correlate with worse atopic state. There are 2-4 fold variations in serum IgE levels with seasonal allergic rhinitis from spring or summer pollens(46) or ragweed pollen (47). Peak IgE levels are usually reached about 4-6 weeks after the peak pollination period and then decline to a nadir just prior to the subsequent pollination season .Higher IgE level always correlates with a bad clinical features and a more resistance to treatment. c) Gender, Poor response in females may be because of, hormonal changes, more allergen exposure to females (agricultural areas depend mainly on female work). These are leading to many exacerbations which in turn leading to a more chronic symptoms with a more severe condition and a more resistance to treatment. d) Perennial type which is the year round exposure to allergen leads to more nasal hyperreactivity with a more severe cases due to non specific hyperactivity that leads to chronic disease with a more stubborn to treatment. f) High percentage of atopic family history: This makes the patients more vulnerable to allergic disorders at earlier ages than non atopic families patients. Earlier disease, mainly leads to more severe attacks in the future, because more nasal hyper reactivity, high IgE level and multiple allergic disease may happen. g) Older ages: They have more nasal hyper reactivity which is due to more allergen exposures and more attacks, in addition to more chronic disease which leads to non specific stimulation of nasal mucosa which in turn leads to more stubborn to treatment.

Treatment cessation lead to high rate of recurrence rate. However, the rate of recurrence was more in mild group as compared to moderate and severe group. This variation was a

reflection of the better response to treatment in mild as compared to other two groups. Thus the response to treatment with black seed oil was severity driven.

The side effects of *N. sativa* extract used in allergic rhinitis was considered trivial as compared with conventional drugs used for allergic rhinitis like steroids or even antihistamines. One of these side effects of systemic *N. sativa* use was mild diarrhea which did not affect the administration of the herb. Excessive nasal dryness was much more in topical use; this may be due to more potent anti cholinergic effect in topical use than systemic use.

6. Conclusions

Systemic use of *N. Sativa* extract is effective in mild and moderate allergic rhinitis symptoms. Factors that may influence the response to systemic N.S treatment in allergic rhinitis include; multiple allergic diseases with high serum IgE level and atopic family diathesis, gender, perennial type, old age group patients. Side effects of *N. Sativa* extract use are trivial and easily controlled. *Nigella sativa* extract has proved to have a strong therapeutic effect in allergic rhinitis.

7. Recommendations

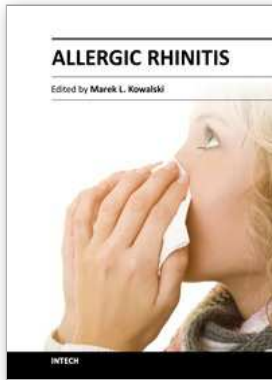
N.S extract oil has proved to be very effective in the treatment of AR so it is recommended as adjuvant therapy in patients treated with immunotherapy or conventional treatment. Conduction of long period treatment course clinical trial to elaborate the recurrence rate is warranted. To plan and conduct studies of longer periods and higher doses to clarify the therapeutic effect of this herb.

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Allergic rhinitis, while troublesome for a patient, may be also a challenge for the physician. That is why physicians must still learn more on the pathophysiology, clinical spectrum and novel diagnostic and therapeutic approaches to the disease. The chapters of this volume address a variety of important topics related to allergic rhinitis. They begin with a description of innovative translational approaches allowing for unification of animal and human models. Contributing authors provide up-to-date reviews of clinical aspects of allergic rhinitis in children, its association with bronchial asthma and other co-morbid conditions. They also discuss the impact of allergic rhinitis on sleep and sports. Together with articles on diagnostic approaches as well as novel treatments, the book offers a comprehensive and stimulating review of the topic. May this book find a wide readership among allergists and other physicians interested in allergic disease, and also among pediatricians, general practitioners and other specialists who increasingly have to deal with this seemingly benign, but sometimes extremely troublesome, disease.

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