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Pharmacological study of a Unani compound formulation in Iltehab Tajaweefe Anaf Muzmin (CRS) patients

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Abstract
The present trial was undertaken to study the pharmacological effects of a Unani Compound Formulation with inhalation of Kalonji and its safety in CRS patients.
In this randomized, single-blind, standard controlled trial, 75 CRS patients were randomly allocated to three groups. In Group A, Unani oral compound formulation of *Katan* (*Linum usitatissimum*), *Filfil Siyah* (*Piper nigrum*) & *Asl-e-Khalis* (Honey)-6gm BD with steam inhalation of Kalonji (*Nigella sativa*), in Group B, the same oral formulation in same dose with steam inhalation, and in Group C, Tab Alaspan 1OD with Karvol Plus inhalation was given. Patients were investigated in the lab for haematological and safety parameters like CBC with ESR, AEC, IgE, LFT, and KFT before and after six weeks of treatment.
The statistical analysis of the data generated was performed by using paired T-test. The results of the data of 60 patients who completed the study show that the test drug has statistically significant anti-inflammatory and antiallergic effects which help to resolve CRS. The formulation is safe as there was no statistically significant effect on safety parameters.
The formulation has significant anti-inflammatory and anti-allergic effects in CRS patients. A multicentric trial of the test drug on larger sample size for a longer duration is required to establish the pharmacological effects of the formulation on CRS patients.

Keywords: Katan, filfil siyah, kalonji inhalation, CRS, anti-inflammatory, anti-allergic

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. Standard Medical Treatment of CRS comprising antibiotics, decongestants drops, antihistaminic and mucolytic agents on long term usage results in many side effects i.e. drug resistance, allergic reactions, altered normal flora of the intestine [1, 2].
In some cases of CRS; surgery is recommended but in 20% of cases revision surgery is needed [2, 3].
In the US as per an earlier estimate by the 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 that there was a loss of 21.2 household days/year due to daily sinus care requirements with an annual productivity cost of $10,077.07 per patient in the USA [2, 4].
The use of herbal medicines and phytonutrients or nutraceuticals continues to expand rapidly across the world with many people now resorting to these products for the treatment of various health challenges in different national health-care settings [5].
Although some herbal medicines have promising potential and are widely used, many of them remain untested and their use is also not monitored. This makes knowledge of their potential adverse effects very limited and identification of the safest and most effective therapies as well as the promotion of their rational use more difficult [6].
Though Unani Medicines are almost safe for human use and effective in the treatment of various diseases as they are based on the thousands years of clinical experience of Unani Physicians but it lacks evidence on modern parameters. To generate new evidence on modern parameters; A randomized, single-blind, standard controlled study of a Unani oral compound formulation of *Katan* (*Linum usitatissimum*), *Filfil Siyah* (*Piper nigrum*) & *Asl-e-Khalis* (Honey) with steam inhalation of *Kalonji* (*Nigella sativa*) from classical Unani literature was undertaken to assess the safety, efficacy, and its possible pharmacological effect in *Iltehab Tajaweefe Anaf Muzmin* (CRS) patients [7].

In classical Unani medical literature the pharmacological properties of *Katan*, *Filfil Siyah*, *Asl-e-Khalis* and *Kalonji* the ingredients of the formulation have been described as *Mohallil-e-Auram* (anti-inflammatory) besides other properties [8, 9, 10].

In some of the pharmacological/clinical studies the results shows that *Katan* (Linum usitatissimum) pharmacological/clinical studies the results shows that *Katan* (*Linum usitatissimum*) has potential anti-inflammatory and antibacterial properties [11, 12]. It has been also proven that the other ingredient *Filfil Siyah* (*Piper nigrum*) to possess the potential anti-inflammatory, antibacterial, antifungal, and immune-suppressant activities besides its action of enhancing the bioavailability of medicines in blood as per the results of the scientific studies [13].

In some pharmacological/clinical studies, it has also been proved that Honey has potential antibacterial activity [14]. After an in-vitro study, *Nigella sativa* has shown preventive effects on tracheal response and lung inflammation in guinea pigs exposed to Sulfur Mustard [15]. In a comparative clinical study it was concluded that steam inhalation with *Nigella sativa* has been more effective than Chamomile in relieving symptoms of Chronic Bronchial Asthma [16]. In a double-blind clinical study, findings are consistent with evidence that *N. sativa* has anti-allergic effects [17].

Material and Methods

Study design

The present prospective study was carried out during July 2014-June 2015 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, standard controlled trial. The patients of Chronic Rhinosinusitis 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 [2, 18].

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 six 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 enrolling the patients for the study [2].

Inclusion Criteria

Chronic rhinosinusitis patients of both sexes between 18-75 years of age with impaired quality of life, as measured by the Rhinosinusitis Disability Index (RSDI) and willing to participate in the study were included in the study.

The patients were excluded from the study on the basis of i.e. Pregnancy, Diabetes mellitus, Hepatic Failure, CRF. Patients with use of any other investigational agent in the last 30 days and chronic or intermittent use of inhaled, oral, intramuscular, intravenous, and/or potent Steroids were excluded from the study [2, 19].

The patients were taken as withdrawal cases during study on the basis of i.e. Failure to follow the protocol, any adverse reaction or adverse event and drug defaulters [2].

Test drug

Composition of the oral drug:

1. *Katan* (*Linum usitatissimum* Linn.) 10.0gm/day
2. *Filfil Siyah* (*Piper nigrum* Linn.) 2.0gm/day
3. *Asl-e-Khalis* (Honey) 10.0gm/day

Kalonji (*Nigella sativa* Linn) for steam inhalation. [20]

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 vouchers of all the crude drugs identified were deposited in the lab for future reference (Reference number; PL/JH-001547/2014/5/6/7/8). The granules dosage form was prepared as per the method prescribed in classical Unani literature.

Control drug

Composition of Tablet Alaspan AM
Loratadine 5 mg
Ambroxol 60 mg
Capsule Karvol Plus for inhalation (Indoco Remedies Ltd)

Dose and Administration

Group A (Test Drug Group): The patients were instructed to take oral medication 6.0 gm BD after the meal. *Kalonji* 5gm was given to the patients with instructions for pounding than boiling it in water and inhaling its medicated steam after covering the head and face with a towel for 10 minutes BD [2, 7, 16, 20].

Group B (Test Drug Group): The patients were instructed to take oral medication 6.0 gm BD after the meal and to inhale the water steam after covering the head and face with a towel for 10 minutes BD.

Group C (Control Drug): The patients were instructed to take Alaspan AM 1Tab OD and to put Capsule Karvol Plus contents in boiled water and to inhale its steam after covering the head and face with a towel for 10 minutes BD [2].

Participants

Seventy five patients who fulfilled the inclusion criteria as per the protocol and consented to participation were taken for study and were randomly allocated to the three groups. Guidelines for conducting clinical trials like Good Clinical Practices (GCP) and the 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”.

Laboratory Procedures

Complete Blood Count (CBC) with Erythrocytes Sedimentation Rate(ESR), Immunoglobulin E (IgE 0-10=Low, 10-100=Normal, 100> = Elevated), Absolute Eosinophils Count (AEC), Liver Function Tests (LFT), Kidney Function Tests (KFT), X-ray Chest-Postero-anterior view, CT scan Para Nasal Sinuses, Nasal Swab culture, and sensitivity test & cytology, Electro Cardio Cardiogram (ECG), Urine R/M were performed on day 1 and 42 [2, 18].

The selected patients were given medication for one 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.

Table1: Patients Follow-up Schedule

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

Randomization

All the eligible patients were randomized to three parallel groups; test drug group (Group A) with inhalation of *Kalonji* steam, test drug group (Group B) with inhalation of steam,

and control group (Group C). The statistician generated a randomized list with the help of the block randomization method. The Assistant assigned the patient to the three groups as per the randomized list. The medical staff and patients were blind to the way of randomization.

Outcome

Effect of treatment on haematological parameters

Assessment of the effect of test drug and control drug on the haematological parameters was based on the laboratory tests done before and after 6 weeks of treatment.

Effect on Safety parameters

Assessment of the safety of test drug and control drug on the LFT and KFT was based on the test done before and after 6 weeks of treatment.

The statistical analysis was done by using paired T-test by comparing the mean of the test data before and after 6 weeks of treatment.

Results and Discussion

The 60 patients of CRS completed the 6 weeks study period with 20 patients in each group**.**

Effect of test and control drugs on haemoglobin

After treatment, there was statistically significant decrease in the Mean haemoglobin level in both test drug groups (A & B). (p<.05)

Effect of test and control drugs on Total Leucocytes Count (TLC)

After treatment, there was statistically non-significant drop off in the Mean of TLC in both test drug groups (A & B) and Control group C.

Effect of test and control drugs on neutrophils

After treatment, there was statistically non-significant rise in the Mean of Neutrophils in test drug group A, and decrease in groups B & C.

Effect of test and control drugs on lymphocytes

After treatment, there was statistically non-significant drop off in the Mean of Lymphocytes in the test drug group A with an increase in the test drug group B. There was no change in control group C.

Effect of test and control drugs on eosinophils

After treatment, there was statistically non-significant decrease in the Mean of Eosinophils in both test drug groups (A & B) and also in the control group C.

Effect of test and control drugs on basophils/monocytes

After treatment, there was statistically non-significant decrease in the Mean of Basophils/ Monocytes in both test drug groups (A & B) and control group C.

Effect of test and control drugs on ESR

After treatment, there was a decrease in the Mean of ESR along with the groups (A, B & C) which were statistically significant. (Table 2)

Effect of test and control drugs on LFT, and KFT

There was effect of the treatment on different safety parameters of LFT and KFT in test groups (Groups A & B) and control group (Group C) but did not show any significant statistical difference. (Table 4)

Table 2: Effect of Treatment on haematological parameters of CRS patients in group A, B & C

Haem-atological Parameters	Group A			Group B			Group C		
	BT Mean ± SD	AT Mean ± SD	*p* Value	BT Mean ± SD	AT Mean ± SD	*p* Value	BT Mean ± SD	AT Mean ± SD	*p* value
Hb%	13.435 1.221	12.94 1.595	.0400 S	13.575 1.393	13.17 1.29	.016 S	13.12 1.476	12.96 1.182	.1272 NS
TLC	7349.5 1555.0	6735.0 1367.2	.0898 NS	6657.5 1769.5	6295.0 1283.2	.290 NS	7732.5 1400.4	7133.0 1942.1	.178 NS
Neutro Phils	58.5 7.896	61.8 6.485	.0608 NS	63.4 4.4	61.45 4.48	.263 NS	63.5 5.67	60.5 10.3	.208 NS
Lympho Cytes	31.65 5.694	30.8 6.225	.2462 NS	28.5 6.22	30.75 4.83	.146 NS	29.9 5.42	29.7 6.95	.916 NS
Eosino Phils	5.666 2.336	5.55 1.8488	.216 NS	6.0 4.83	5.6 1.39	.464 NS	5.5 2.35	4.2 0.95	.005 NS
Baso phils Mono Cytes	2.4 1.14	1.85 1.0894	.094 NS	2.1 1.07	1.75 1.11	.309 NS	1.5 0.89	1.4 1.14	.635 NS
ESR	23.25 6.677	21.05 6.232	.0386 S	22.95 5.014	20.25 5.30	.0398 S	21.35 7.611	18.2 5.758	.0008 S

BT=Before Treatment, AT= After Treatment, SD= Standard Deviation, Hb=Haemoglobin
S=Significant, NS=Non Significant, *p* value significant at <0.05

Table 3: Effect of Treatment on AEC and IgE of CRS patients in Group A, B & C

Haem-atological Para-meters	Group A			Group B			Group C		
	BT Mean ± SD	AT Mean ± SD	*p* Value	BT Mean ± SD	AT Mean ± SD	*p* Value	BT Mean ± SD	AT Mean ± SD	*p* value
AEC	484.65 442.19	350.00 115.54	.1018 NS	411.6 272.92	340.00 126.57	.133 NS	397.1 214.4	313.0 172.02	.008 NS
IgE	592.06 1225.293	192.05 266.6495	.0411 S	423.58 597.20	159.44122.00	.095 NS	162.4 127.4	71.405 46.235	.0003S

BT=Before Treatment, AT= After Treatment, SD= Standard Deviation
S=Significant, NS=Non Significant, *p* value significant at <0.05

Table 4: Effect of Treatment on Safety Parameters of CRS patients in Group A, B & C

Safety Parameters (LFT & KFT)	Group A			Group B			Group C		
	BT Mean ± SD	AT Mean ± SD	*p* Value	BT Mean ± SD	AT Mean ± SD	*p* Value	BT Mean ± SD	AT Mean ± SD	*p* Value
Total Serum Bilirubin	0.53 35.11	0.51 0.17	.079 NS	0.605 0.233	0.59 0.35	.033 NS	0.56 0.30	0.52 0.22	.254 NS
SGOT	34.06 16.86	30.26 14.09	.180 NS	29.85 9.01	29.15 15.41	.290 NS	25.75 9.28	26.45 9.38	.178 NS
SGPT	53.22 44.16	51.70 40.66	.134 NS	40.05 17.32	40.4 13.57	.263 NS	59.10 14.08	40.80 12.93	.208 NS
Serum Alkaline Phosphatase	115.49 35.11	112.2 6 29.86	.493 NS	105.61 27.14	110.0 21.82	.146 NS	114.6 5 31.98	112.55 33.84	.916 NS
Blood Urea	18.59 7.89	21.47 7.61	.216 NS	19.109 8.404	22.6 6.25	.464 NS	22.20 7.57	22.05 8.64	.8557 NS
Serum Creatinine	0.68 0.14	1.121 1.37	.094 NS	0.762 0.186	0.79 0.199	.309 NS	0.73 0.23	0.71 0.19	.635 NS
Serum Uric Acid	5.24 1.35	4.82 1.21	.204 NS	4.7385 1.0110	4.99 1.473	.133 NS	4.42 1.22	4.31 1.13	.9499 NS

BT=Before Treatment, AT= After Treatment, SD= Standard Deviation
S=Significant, NS=Non Significant, *p* value significant at <0.05

After treatment, there was no significant change in parameters of haemogram either in all the three groups (Table 2), except for both the test groups wherein haemoglobin levels fell to a statistically significant level after treatment which perhaps was due to the oral test drug Flaxseed as evidenced through earlier studies [21].

ESR also decreased in all three groups, (Table 2) which was statistically significant indicating the effectiveness of the test drugs as well as the control drug.This was due to the anti-inflammatory action of the *Katan* (*Linum usitatissimum*) the main ingredient of the formulation [11, 21, 23], *Filfil Siyah* (*Piper nigrum*) [24, 26] in test drug groups (A & B), and in group C of Ambroxol [27].

The decrease in IgE level in group A may be attributed to the antihistaminic effect of *Nigella sativa* as nigellone contains flavonoids that efficiently inhibit the production of prostaglandins and leukotrienes from arachidonic acid because they block cyclo-oxygenase and lipoxigenase rl8lq [17, 28, 29, 30, 31].

In group C, it may be due to antihistaminic effect of Loratadine [27].

After treatment results did not show any statistically significant difference in the safety parameters hence the test drug is safe and did not raise any safety issue. Moreover, this formulation has been found as an effective and safe regimen in the treatment of Chronic Rhinosinusitis a chronic inflammatory disease after clinical trial [2]. This study also approves *Mohallil-e-Auram* (Anti-inflammatory) the main pharmacological property of the ingredients of compound formulation; *Katan, Filfil Siyah, Asl-e-Khalis* and *Kalonji* as per the claims of Unani classical literature [6, 7, 8].

Conclusion

From the data analyses of the lab investigations like CBC with ESR, AEC, IgE, LFT, and KFT before and after treatment of six weeks it may be concluded that the test drug has anti-inflammatory and antiallergic effects which help to resolve chronic rhinosinusitis-a chronic inflammatory disease with a component of allergens as a causative factor in its pathogenesis [32]. It may also be concluded that the test Unani compound formulation is a safe regimen in CRS patients as there was no statistically significant effect on safety parameters. A multicentric trial of the test drug on larger sample size for a longer duration is required to establish the pharmacological effects of the formulation on CRS patients.

Conflict of interest

The author hereby declares no conflict of interest.

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References

1. Kennedy DW, Kuhn FA, Hamilos DL, Zinreich SJ, Butler D, Warsi G, *et al*. Treatment of chronic rhinosinusitis with High-dose oral Terbinafine: a double-blind, placebo-controlled study. Laryngoscope. 2005;115 (10):1793-99. https://doi.org/10.1097/01.mlg.0000175683.81260.26
2. Zaidi Z, Khan AA, Jabeen A. Single Blind, Randomised, Control Trial of A Unani Compound Formulation in Iltehab Tajaweefe Anaf Muzmin. Asian Journal of Pharmaceutics and Clinical Research. 2021;14(1):171-75.
3. Hopkins C, Browne JP, Slack R, Lund V, Topham J, Reeves B, *et al*. The national comparative audit of surgery for nasal polyposis and Chronic Rhinosinusitis. Clin Otolaryngol. 2006;(5):390-8.DOI: 10.1111/j.1749-4486.2006.01275.x
4. Luke Rudmik, Timothy L Smith, Rodney J Schlosser, Peter H Hwang, Jess C Mace, Zachary M Soler, *et al*. Productivity cost in patients with refractory chronic rhinosinusitis. Laryngoscope. 2014;124(9):2007-12. DOI: 10.1002/lary.24630.
5. Anonymous. WHO Guidelines on Safety, Monitoring of Herbal Medicines in Pharmacovigilance Systems. Geneva, Switzerland: World Health Organization; c2004. DOI: https://doi.org/10.1016/j.tifs.2014.03.011
6. Anonymous. Traditional Medicine Strategy. WHO/EDM/TRM/2002.1.Geneva, Switzerland: World Health Organization; c2002-2005.
7. Jurjani AH, Zakhira Khwarizm Shahi. Urdu Translation by Hkm.H H Khan, Matba Munshi Nawal Kishore. Lucknow. 1903;2(4):205-6.
8. Ibne Baiytar. Aljame Almufredat Al Adviya Wal Aghziya (1248)-Urdu Edition. CCRUM, New Delhi. 2015;2:228-31,377-79.

9. Sina BA. (1030AD): Alqanoon Fil Tibb-Urdu Edition by G H Kantoori, Munshi Nawal Kishore Press, Lucknow. 1886;3:702-03
10. Baghdadi IH. (1368 H): Al Mukhtarat fittib-Urdu Edition, CCRUM, New Delhi; c2005, 226-27, 268.
11. Shim YY, BoGui, Paul G Arnison, Yong Wang, Martin JT Reaney. Flaxseed (*Linum usitatissimum*) bioactive compounds and peptides nomenclature: A review. Trends in Food & Technology. 2014;38(1):5-20.
12. Tehrani MHH, Mohammad Hassan, Rumeysa Batal, Mohammad Kamalinejad, Arash Mahboubi. Extraction and purification of proteins of Flex seeds and studying their antibacterial activities. Journal of Plant Science. 2014;2(1):70-76. DOI: 10.11648/j.jps.20140201.21
13. Reshmi Karthiga, Sathya E, Suganya Devi P. Isolation of Piperidin from *Piper nigrum* and its anti-proliferative activity. African Journal of Pharmacy and Pharmacology 2010;4(8):562-573. DOI: DOI: 10.5897/JMPR10.033
14. Manisha Deb Mandal, Shyamapada Mandal. Honey: its medicinal property and antibacterial activity. Asian Pac J Trop Biomed. 2011;1(2):154-160. DOI: 10.1016/S2221-1691(11)60016-6
15. Mohammad Hossein Boskabady, Nassim Vahedi, Sediqa Amery, Mohammad Reza Khakzad. The effect of *Nigella sativa* alone, and in combination with dexamethasone on tracheal muscle responsiveness and lung inflammation in sulfur mustard exposed guinea pigs. Journal of Ethnopharmacol. 2011;137(2):1028-34. DOI: 10.1016/j.jep.2011.07.030
16. Faruk H Al-Jawad, Rafi Am Al-Razzuqi, Hashim M. Hashim, Ahmad H Ismael. Broncho- relaxant activity of *Nigella sativa* versus Anthemis nobilis in chronic bronchial asthma; a comparative study of efficacy. IOSRPHR Journal of Pharmacy. 2012;2(4):81-3.
17. Soheila Nikakhlagh, Fakher Rahim, Faezeh Hossein Nejad Aryani, Amir Syahpoush, Mehri Ghafouryan Brougerdnya, Nader Saki *et al*. Herbal treatment of allergic rhinitis:the use of *Nigella sativa*. Am J Otolaryngol. 2011;32(5):402-7. DOI: 10.1016/j.amjoto.2010.07.019
18. Michael S. Benninger, Berrylin J Ferguson, James A Hadley, Daniel L Hamilos, Michael Jacobs, David W Kennedy *et al*. Adult chronic rhinosinusitis: Definitions, Diagnosis, epidemiology and pathophysiology. Supplement to Otolaryngology-Head and Neck Surgery. 2003;129(3 Suppl):S1-S32. DOI: 10.1016/s0194-5998(03)01397-4
19. Naclerio MR. Xolair in patients with chronic sinusitis. Clinical Trials.gov, US National Institute of Health, University of Chicago; c2013. https://clinicaltrials.gov/ct2/show/NCT00117611 (Last verified on September 2013)
20. Mohammad Kabiruddin. Moalejat; Sharah Asbab, 9th Edition. Hikmat Book Depo; Hyderabad. 1980;1:15-20.
21. Ludmila FMF Cardozo, Lavínia L Soares, Maurício A Chagas, Gilson T Boaventura. Maternal consumption of Flax seed during lactation affects- Weight & Haemoglobin level of offspring in rats. J Pediatr (Rio J). 2010;86(2):126-30. DOI:10.2223/JPED.1976.
22. Paul Kinniry, Yassine Amrani, Anil Vachani, Charalambos C Solomides, Evguenia Arguiri, *et al*. Dietary Flaxseed supplementation Ameliorated inflammation and Oxidative Tissue damage in experimental models of Acute Lung Injury. Journal of Nutrition. 2006;136(6):1545-51. DOI:10.1093/jn/136.6.1545.
23. O'Neil W, McKee S, Clarke AF. Flax Seed (*Linum usitatissimum*) supplementation with reduced skin test lesional area in Horse with Culicoides hypersensitivity. Can J Vet Res. 2002;66(4):272-77.
24. Koosha Ghazi-Moghadam, Hasan Mete Inançlı, Nazanin Bazazy, Peter K. Plinkert, Thomas Efferth, Serkan Sertel. Review: Phytomedicine in Otorhinolaryngology and Pulmonology: Clinical Trials with Herbal Remedies. Pharmaceuticals (Basel). 2012;5(8):853-874. DOI: 10.3390/ph5080853
25. Md. Shahab Uddin, Nuri ZN. Therapeutic use of *Nigella sativa*: A review. Int. J Hortic Food Sci. 2021;3(1):06-12.
26. Pratibha N, Saxena VS, Amit A, D'Souza P, Bagchi M, Bagchi D. Anti-inflammatory activities of Aller-7, a novel polyherbal Formulation for allergic rhinitis. Int J Tissue React. 2004;(1-2):43-51.
27. Peroni DG, Moser S, Gallo G, Pigozzi R, Tenero L, Zanoni L, *et al*. Ambroxol inhibits neutrophils respiratory burst activated by alpha chain integrin adhesion. International J. Immuno Pathol Pharmacol. 2013;26(4):883-87. DOI: 10.1177/039463201302600406
28. El-Dakhakhny M, Barakat M, El Halim MA, Aly SM. Effects of *Nigella sativa* oil on gastric secretion and ethanol induced ulcer in rats. J Ethnopharmacol. 2000;72(1-2):299-304. DOI: 10.1016/s0378-8741(00)00235-x
29. Ulrich Kalus, Axel Pruss, Jaromir Bystron, Moric Jurecka, Alice Smekalova, Johannes Josef Lichius *et al*. Effect of *Nigella sativa* (black seed) on subjective feeling in patient with allergic diseases. Phytother Re. 2003;17(10):1209-14. DOI: 10.1002/ptr.1356
30. Ali E Al-Snafi, Abdul Ghani M Al-Samarai, Ahmed M Al-Sabawi. The Therapeutic Effect of *Nigella sativa* seed oil in treatment of chronic Urticaria. Tikrit Journal of Pharmaceutical Science. 2005;1(1):1-6.
31. Elahi Homayoon, Mohammad Reza Masroorchehr, Shadman Nemati, Mohammad Kamalinejad, Mehdi Besharat, Homa Hajimehdipoor *et al*. Historical Applications of *Nigella sativa* L. (Black cumin) in the Treatment of *Zokam* and *Nazleh* in Persian Medicine. Res Hist Med. 2014;3(1):11-20.
32. Richard M. Rosenfeld, David Andes, Neil Bhattacharyya, Dickson Cheung, Steven Eisenberg, *et al*. Clinical practice guidelines: Adult Sinusitis. Otolaryngol Head Neck Surg. 2007;137(3Suppl)25:S1-31. DOI:10.1016/j.otohns.2007.06.726.000000.