



## A randomized, double blind clinical trial of commercial garlic on improvement of lung functions in asthmatic patients

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### Abstract

Bronchial asthma is characterized by both a decline in lung functions and periods of acute deterioration in symptoms called exacerbations. The aim of this study was to investigate the effects of garlic on lung functions in acute exacerbations in asthma. Asthma patients attending to the clinic were randomized into 2 groups. One group was given commercial garlic and other group was given the placebo (900mg /day) for 3 months and followed by 2 months of drug free interval. Treatment was continued again for next 2 months and lung functions were assessed during the follow up. Clinical status of the asthma was assessed using asthma symptom score. There was a significant difference in vital capacity (VC), Forced vital capacity (FVC), forced expiratory volume (FEV1), peak flow rate (PFR) and mid expiratory flow rate (MEFR) in garlic treated group but not in control group. Addition, there was a statistically significant difference in increase of FEV1/FVC ratio only in test group. Reduction of air trap in lungs was significant in test group compared to the control. VC, FVC, FEV1 and PFR values were static during the drug free period and increased again with the commencement of the therapy, in garlic group. Our data suggests that therapeutic effect of garlic is rapid in onset and have long lasting effects on bronchial relaxation. Beneficial effects observed with garlic therapy in asthma patients can be explained by effects as muscle relaxant, anti-inflammatory and immune modulator effects caused by garlic.

Keywords: garlic, bronchial asthma, immune modulation

### Introduction

Bronchial asthma is a reversible obstructive airway disease characterized by paroxysms of breathlessness, tightness of chest, wheezing due to combination of muscle spasm, mucosal swelling and viscid bronchial secretions<sup>1</sup>. Patients with asthma have increased number of inflammatory cells like monocytes, eosinophils and lymphocytes in the airways<sup>2</sup>. Several studies of asthmatic patients reveal that leukotrienes increase vascular permeability, mucosal oedema, mucous production, airway responsiveness and also bronchoconstriction in asthmatic patients<sup>3-6</sup>.

There is compelling evidence that immune mechanisms are involved in causation of asthma<sup>7-9</sup>. The direct relaxant effect of garlic on smooth muscles<sup>10</sup>, the anti-cholinergic effects and inhibitory effects on calcium dependant-tonic contractions of tracheal muscles can relax the bronchial smooth muscles and could be beneficial in relieving asthmatic symptoms<sup>10</sup>. Further, immuno-modulating effects on lymphocytes and antioxidant effect of garlic which

cause the arachidonic acid release from inflammatory cells, were also considered as beneficial in asthma. The direct relaxant effect of garlic on smooth muscles, the anti-cholinergic effects and inhibitory effects on calcium dependant-tonic contractions of tracheal muscles are considered as beneficial in relieving asthmatic symptoms<sup>10-15</sup>. Further, T<sub>1</sub> cell inflammatory cytokine production is reduced by garlic extracts revealing the potential therapeutic use in inflammatory diseases like asthma<sup>13</sup>. Antioxidant effect of garlic which inhibit the pro-inflammatory inducible nitrite oxide synthase production are also considered as beneficial in asthma<sup>14</sup>. As there are no reported studies to prove the beneficial effects of garlic on lung functions, this is the first ever pioneering study in this respect.

This study reports that a decline in incidences of exacerbations in asthmatic patients. We also report that garlic has significant reducing effects on preventing bacterial infections in asthmatic lungs avoiding acute exacerbations. This improves the life style of the

asthma patients and avoids recurrences and exacerbations.

### Materials and methods

The research protocol was submitted to the Ethics Committee in the Faculty of Medicine University of Ruhuna and approval was obtained prior to the commencement. The consent form was prepared in the Sinhala language and written consent was obtained for each study after full explanation of the test and its method, risks and benefits to the patient. The tested garlic capsule is a commercial product. It is available in the market as a commercial product. It was obtained from the “Unical” manufacturing company (analysis report is available). Each capsule contains 300 mg of *Allium sativum*. Placebo capsules were manufactured by the same Company and were prepared to resemble the available garlic capsule in order to minimize the bias of both patient and the investigator. Each capsule contains 300 mg of *Allium sativum*.

#### Inclusion criteria

Patients were selected from the medical clinics in Teaching Hospital, Galle. Selection of participants; the nature and the purpose of the study were explained to the patients and written consent was obtained. Current medications and disease status were recorded. Patients between 25–60 years who were taking oral anti-asthmatic drugs were selected after obtaining informed written consent. 80 patients were allocated into two groups by alternate assignment. Odd numbered patients were allocated to the garlic group and even numbered were allocated to the placebo group.

#### Exclusion criteria

Participants who had an occupation requiring heavy physical activity, smokers, alcoholics pregnant and

lactating mothers were excluded. Patients with frequent hospitalizations for exacerbations and complications with other illness were excluded. Lung functions were measured using Pulmotester (SHIMARU, Japan).

#### Pulmonary function test

Pulmonary function test (PFT) was performed on all the patients before the therapy. Each patient had a spirometry analysis of forced expiratory volume in first second (FEV1), forced vital capacity (FVC), vital capacity (VC), peak expiratory flow rate (PEFR), mid expiratory flow rate (MEFR) and air trapping. The entire test was standardized according to the American thoracic society criteria.

After the general examination, they were kept for 15 minutes for relaxation and lung functions were conducted. Patient was kept in upright position to perform easy breathing and brief explanation on the examination was given. PFT was repeated three times and best value was selected for analysis. For calculation of air trapping, following equation was used according to the manufacture's protocol.

$$\text{Index of air trapping} = \frac{\text{Vital capacity} - \text{Forced vital capacity}}{\text{Vital capacity}} \cdot 100\%$$

#### Asthma Symptom Score

Participants were assessed clinically by using the following standard asthma symptom score. Table 1 shows the criteria of standard day and night asthmatic score system. The score was recorded at each visit. Patients were examined routinely for the following parameters. Height and weight were measured by a Medical officer. Same scales were used throughout the study.

Table 01 description of the asthma symptom score

	Night symptom score	Day symptom score
0	No symptom during night	No symptom
1	Symptoms causing awake one	Symptoms for short period
2	Symptoms causing awake twice or more	Symptoms for two or more short period
3	Symptoms causing to be awaked in most of the nights	Symptoms occur most of the day time but did not affect the day to day activities
4	Did not sleep at all	Severe symptoms preventing work or daily activities

### Treatment

Patients were advised to take one capsule three times a day (one capsule, 300mg of either testing or placebo capsule) for two weeks and assessed at fortnight intervals for three months. After three months patients were kept drug free interval of 2 months and continued the same assessment.

Patients were issued again the treatment packs of garlic as well as placebo and kept on the same doses for second intervention. After second intervention, treatment was discontinued and tested for serum lipid profiles at the end of the second intervention.

### Statistical analysis

Baseline data was compared statistically with those obtained at the 7 months follow-up. The differences of in the values of PFT results were calculated. The descriptive statistics, mean, standard deviation, standard error, 5<sup>th</sup> 95th percentiles and 95 confident intervals were used to describe the findings. The difference between initial and final reading of each parameter for all patients were individually were calculated. Differences between initial and final values were tested at each intervention using paired *t*-test. Wilcoxon's signed rank test was employed to test the difference between initial and the final values due to the non-normality of the distribution of the difference.

Table 03 shows the asthma symptom score, FEV1, VC and FVC in our patients at the baseline. Data are given as M ± SE.

	Garlic <i>n</i> = 20	Placebo <i>n</i> = 20	<i>p</i> value
Asthmatic duration	3.8 ± 1.0yr	3.9 ± 1.0yr	0.814
VC (ml)	1653 ± 18.9	1778 ± 12.8	0.402
FVC (ml)	1315 ± 11.1	1460 ± 18.8	0.152
FEV1 (ml)	1066 ± 9.5	1045 ± 81.3	0.847
PFR (ml)	211 ± 8.2	204 ± 5.9	
Day time ASS	2	1	
Night time ASS	1	1	

There was a significant improvement on VC, FVC, FEV1, MEFV and PFR with commercial garlic in asthma. These values continuously increased during the first intervention in test group and remained static during the drug free interval. Values increased again the second intervention (*p* < 0.05). FEV1 / FVC increased and air trap was reduced with garlic therapy (*p* < 0.05). The placebo treated group also showed the changes of PFT values which were not statistically significant.

### Results

Total of 70 patients were included in this study. They were 40 males and 30 females. Asthmatic symptoms were assessed using day and night asthma symptom score. There were no reported cases in exacerbations and hospital admissions. There was also no difference in long term inhaled steroid use in asthma patients of both groups.

Age and sex distribution and the changes of the initial values of the PFT are given in table 2.

Table 02 basic characteristics of the study groups. M ± SE

Characteristics of individuals	Garlic group	Placebo group
Age	48.0 +/- 3.7	42.6 +/- 3.9
Weight (kg)	58.5 +/- 6.9	53.3 +/- 4.2
Female: male	9 : 4	8 : 5

### Garlic improved lung functions in asthmatic patients

There was no clinically meaningful difference in the demographic parameters or baseline characteristics between the treatment groups. At the beginning of the study, there was no statistical difference between garlic and placebo treated groups (Table 3).

### 1.2 Effects of garlic on vital capacity

There was a significant increase in VC in test group of patients (*p* < 0.001). Kinetic changes in VC were analyzed noticed that values continuously increased during the first intervention in test group and remained static during the drug free interval of two months. Values increased again during the second intervention (Figure 1).

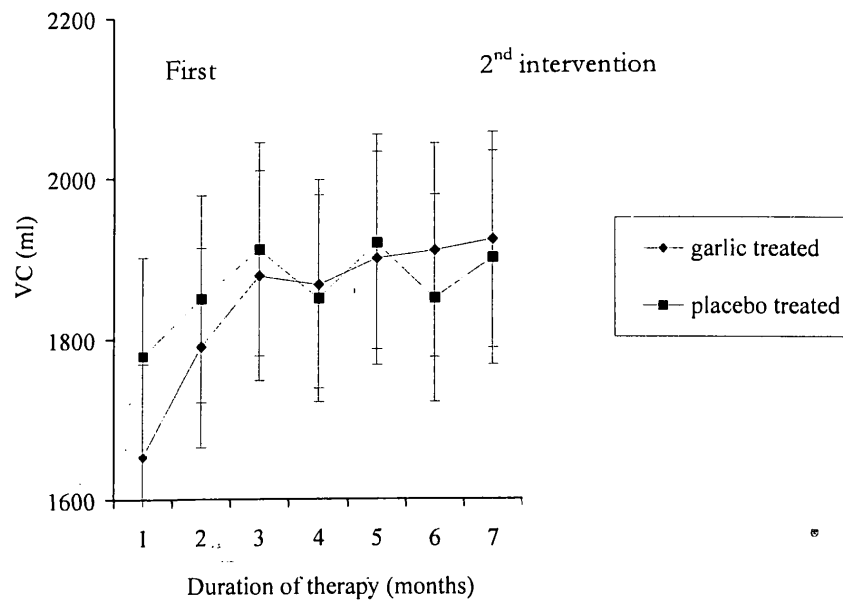


Figure 1 Asthmatic patients were treated by either garlic or placebo for 3 months (1<sup>st</sup> intervention) followed by drug free two month interval and again treated by garlic or placebo for two months (2<sup>nd</sup> intervention). Changes of mean VC values in both garlic and placebo treated groups during the study. Values are given as mean  $\pm$  S.E.M.

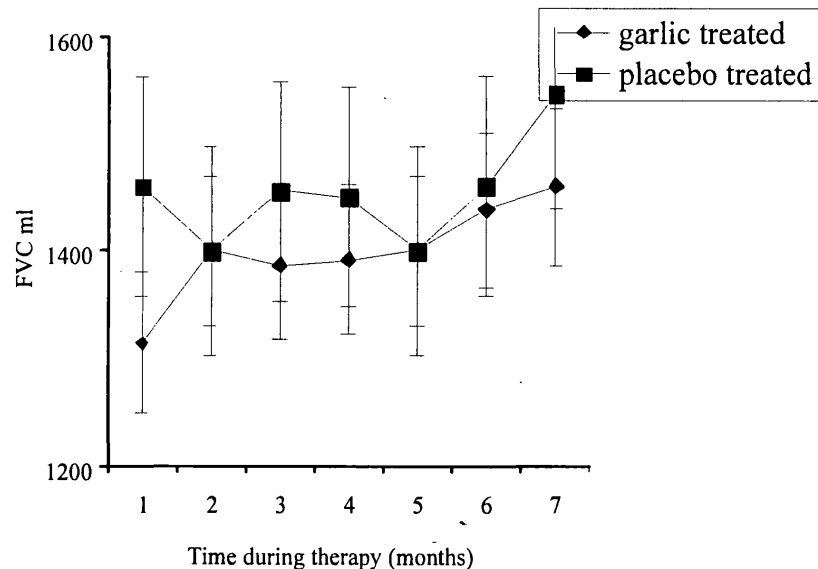


Figure 02 Asthmatic patients were treated by either garlic or placebo treatment for 3 months (1<sup>st</sup> intervention) followed by drug free two month's interval and followed by garlic or placebo for another two months (2<sup>nd</sup> intervention). Kinetic changes of mean FVC values in both garlic and placebo treated groups during the study. Values are given as mean  $\pm$  S.E.M

*Effect of garlic on forced vital capacity*

Results showed that FVC significantly increased with oral garlic therapy in asthmatic patients ( $p = 0.0035$ ,  $p < 0.001$ ) during the first intervention of garlic and remained static during the drug free interval. Values increased again during the second intervention (fig 2). In control group, difference in changes was insignificant ( $p = 0.72$ )

*Effects of garlic on forced expiratory volume 1*

Our results showed that FEV1 significantly increased with commercial garlic ( $p = 0.7292E$ ,  $< 0.001$ ). Kinetic analysis of FVC changes was done and the values continuously increased during the first intervention of garlic therapy. Values increased again during the second drug intervention after 2 months static period of drug free interval. (Changes for control group -  $p = 0.39$ )

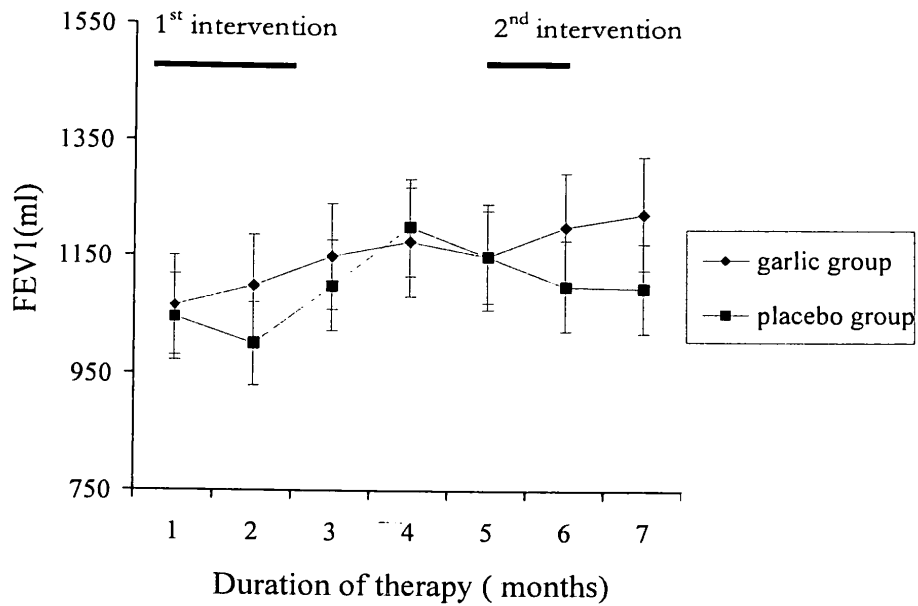


Figure 3. Asthmatic patients were treated by either garlic or placebo treatment for 3 months followed by drug free two months interval and again treated by garlic or placebo for two months. Kinetic changes of mean FEV1 values in both garlic and placebo treated groups during the study. Values are given as mean  $\pm$  S.E.M.

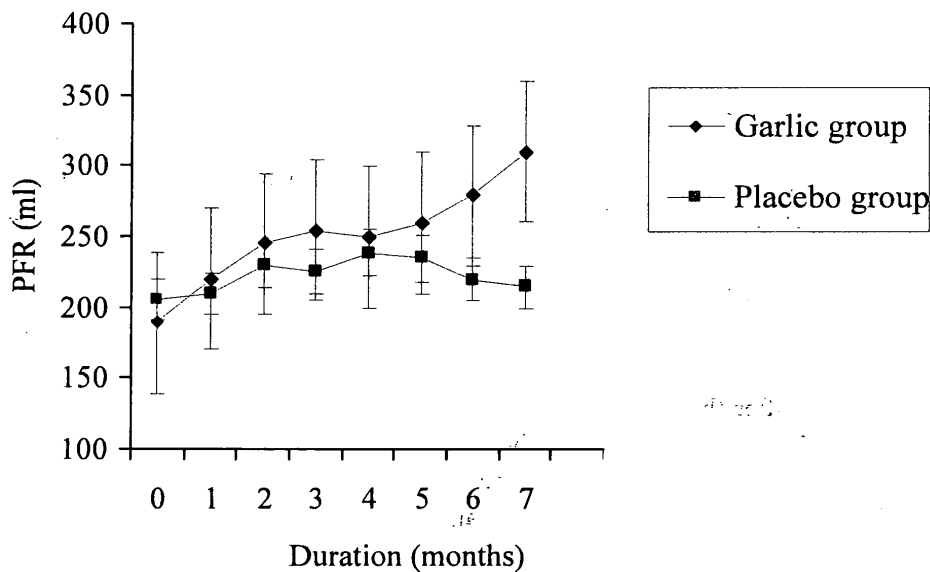


Figure 4. Asthmatic patients were treated by either garlic or placebo treatment for 3 months (1<sup>st</sup> intervention) followed by drug free two months interval and again treated by garlic or placebo for two months (2<sup>nd</sup> intervention). (B) Kinetic changes of PFR values in both garlic and placebo treated groups. Values are given as mean  $\pm$  S.E.M.

*Effects of garlic on peak flow rate*

PFR significantly increased with commercial garlic therapy in asthmatic patients ( $p < 0.001$ ). Kinetic analysis of PFR showed that there was a continuous

improvement during the first intervention of garlic treatment and remained static during the drug free interval. Values were again increased during the second intervention (Figure 4).

*Effects of garlic on FEV1/FVC ratio and air trap in asthmatic patients*

FEV1/FVC ratio and air trap were calculated in garlic and placebo treated asthmatic patients. FEV1, FVC and ratio values were significantly increased with garlic

therapy ( $p < 0.005$ ). In contrast, ratio did not significantly increase in the placebo group. Similarly air trap also significantly increased with garlic but not in placebo group of asthma patients.

Table 4. Values of FEV1/FVC and air trap both in test and control group of patients before and after study. Asthmatic patients were treated by either garlic or placebo treatment for 3 months (1<sup>st</sup> intervention) followed by drug free two months interval and again treated by garlic or placebo for two months (2<sup>nd</sup> interval). Values are given as mean  $\pm$  S.E.

Lung functions	Garlic group		Placebo group	
	Before drugs	After drugs	Before drugs	After drugs
FEV1/ FVC	73.8 $\pm$ 1.3	83.9 $\pm$ 1.3	72.0 $\pm$ 0.6	75.2 $\pm$ 1.7
Air Trap	20.3 $\pm$ 2.2	15.5 $\pm$ 2.1	15.6 $\pm$ 2.9	13.8 $\pm$ 0.9

### Discussion

The effects of garlic on smooth muscles of rat have been tested in *in vitro* isolated segments of aorta, trachea and intestine. Garlic inhibits the contractions of aortic rings induced by norepinephrine, acetylcholine, histamine and spontaneous movements of rabbit intestine and heart muscles in a dose dependent manner<sup>10-11</sup>. It has been reported that garlic has an inhibitory effect on bronchial smooth muscle contractions induced by acetylcholine and histamine<sup>10</sup>.

All the patients selected for this study nearly had same ASS (both day and night 1) therefore minimized the two group variation. Mean values of VC, FEV1, FVC and PFR were not significantly different in test and placebo groups.

Means of VC and PFR after the garlic therapy were significantly increased in garlic treated group. There was no published data regarding clinical trials of garlic therapy in asthma patients. This study has shown that asthmatic patients with moderate chronic obstructive air way disease (COPD) experienced a significant improvement of lung functions. During this study, I found that our study participants in test group did not receive any additional treatments for exacerbations of asthma during study period. There were 13 patients who had hospitalized for the acute exacerbations of asthma in the control group during 7 months. Those patients were excluded from my study. Another study has recently shown that exacerbation frequency is an important independent risk factor for treatment failure.

This data further showed that FVC and FEV1 values were significantly increased at the end of the two

drug intervention periods with garlic therapy. I am not in a position to comment on the clinical significance of this improvement for late consideration for drug development.

There are number of mechanisms that explain the improvement of lung functions with commercial garlic therapy. Presence of bacteria in the airways can cause increased airway neutrophilia, inflammatory markers and persistence bacterial colonization of airways depending on the severity of the underlying airway obstruction. It has been reported that garlic and its purified active compounds such as allicin have antifungal and antibacterial effects by increasing the activity of enzymes such as glutathione S-transferase and super oxide dismutase in rodent brain and liver<sup>16-17</sup>.

Patients with frequent exacerbations of asthma have higher levels of cytokines IL-6 and IL-8 in sputum which suggests that acute episode is associated with increase airway inflammation. Importantly, there are reports showing that garlic has anti-inflammatory effects by altering T lymphocyte cellular immune response at nuclear level. IL-4 is a one of the major target for the new cytokine agent to be used as anti-asthmatic drug because of its anti-inflammatory effects. Garlic also has increased the secretion of IL-4 which is a major anti-inflammatory cytokine in cellular immune responses. Therefore my findings regarding the improvement of asthmatic status are in accordance with the above reports. This confirms that garlic has anti-inflammatory, immunomodulating and antibacterial effects which are beneficial in decline in acute episode of exacerbations due to bronchial inflammation in asthmatic patients.

Interestingly, all these values (VC, FVC, FEV1 and PFR) were remained static during the drug free interval and increased again during the second intervention. This observation suggests that improvement of bronchial obstruction and air way inflammation was long lasted until 8 weeks in the absence of garlic. Addition to the beneficial effects on airway inflammation, there may be other reported mechanisms that can explain this long lasting lung functions. Direct inhibitory effect on contractions of bronchial smooth muscle, adrenergic effects and specially antioxidant properties may contribute to long lasting decline in exacerbation rates and improve the forced expiration in asthmatic patients. One report informed that some components of the herbal plant (*Zizyphi fructus*) have nitric oxide dependant facilitatory action on ciliary motility in respiratory mucosa. As garlic can increase the nitric oxide synthase, I suggest that garlic help in relieving symptoms in asthmatic patients by NO dependant facilitating action on the ciliary motility. All effects together can prevent acute respiratory infections, clear the inflammatory secretions and maintain the bronchus in the relaxed states.

Taken together this data suggest that the long lasting persistent improvement in lung functions with commercial garlic therapy<sup>18</sup> could be due to the synergistic effects from bronchial dilatation, improved ciliary motility and the immuno-modulatory<sup>19</sup> and anti-inflammatory effects. This facilitates easier expiration. This data also showed that FEV1/FVC value was improved with the garlic therapy. Ratio of the FEV1 to FVC indicates the relative improvement of the bronchial obstruction in obstructive airway diseases. When the bronchial inflammation is reduced and the bronchus is relaxed by garlic, the forced expiration capacity is invariably increased. The improvement observed in ratio between FEV1/ FVC also can be explained with these mechanisms. Air trap is an indication of trapping of air with in the lung with resultant of increase of residual lung volume. When the garlic is given to asthmatic patients, I observed that vital capacity is also increased indicating that decrease in residual lung volume improving the maximum expiratory volume. This explains how the air trap is reduced with the garlic therapy in test group compared to the placebo group.

Though there is a statistical significant difference was observed in most of the lung functions, implication on clinical significance remained obscured. Purification and isolation of responsible garlic

compounds which are responsible for the beneficial effects observed in our study may be helpful to pharmacodynamic studies in the development of a drug in the treatment of asthma.

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#### References

1. Bhowmik, A., Seemungal, T. A. R., Sapsford, R.J. 2000. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 55: 114-120
2. Hodge, G., Hodge, S., Hang, P. 2002. Garlic suppresses leukocyte inflammatory cytokine production in vitro; potential therapeutic use in inflammatory diseases. *Cytometry* 48: 209-215.
3. Tamaoki, J., Kondo, M.: (1996) *Zizyphi fructus*, a constituent of anti-asthmatic herbal medicine, stimulates airway epithelial ciliary motility through nitric oxide generation. *Experimental Lung Research* 22 (3), 255-266.
4. Zalacain, R., Sobradillo, V., Amilibia, J. ( 1999) predisposed factors to the bacterial colonization in chronic obstructive pulmonary disease. *European respiratory Journal* 13: 343-348.
5. Croker, I. C., Gupta, K., Townly, R. G., Khan, M. M. 1998. The profile of the cytokines secreted during the generation of T-helper cells from atopic asthmatic subjects. 35(2): 187-201.
6. Lewis, J.: (1996) Leukotrienes in asthma. The potential therapeutic role of anti-leukotrienes agents. *Acta. Internal Medicine*, 56; 156-158.
7. Lewis, J.: (1996) Leukotrienes in asthma. The potential therapeutic role of anti-leukotrienes agents. *Acta. Internal Medicine*, 56; 156-158.
8. Dirsch, V, Gerbes, L.; Ajoene : (1998) a compound of garlic , induces apoptosis in human promyeloleukemic cells, accompanied by generation of reactive oxygen species and activation of nuclear factor kappa B. *Pharmacology*. 53, 402-407.
9. Imai, J, Ide, N. et al: (1994) Antioxidant and radical scavenging effects of aged garlic extract and its constituents. *Planta Medica*. 60, 417-420.
10. Aquel, M., Gharaibah M. et al: (1991) Direct relaxant effects of garlic juice on smooth and cardiac muscles. *Journal Of Ethanopharmacology*. 33, 13-19.

11. Yusuf, O., Suleyman, A.: (1994) Endothelium dependent and independent effects of garlic on rat aorta. *Journal Of Ethnopharmacology*. 44, 109-116.
12. Martin, N., Bardisa, P. et al: (1997) Involvement of calcium depressant actions of a garlic dialysate. *Journal Of Ethnopharmacology* 55, 113-118.
13. Eikai Kyo, Naoto Uda, Shigeo Kasuga and Yoichi Itakura 2001 immunomodulatory Effects of Aged Garlic Extract *Journal of Nutrition*. 2001;131:1075S-1079S
14. Nagatoshi. I. Hiromichi, M., Yoichi I: (1996) Scavenging effects of aged garlic extracts and its constituents on active oxygen species. *Phytotherapy research* 10, 340-341.
15. Geng Z, Rong Y: (1999) S allyl cysteine (garlic) inhibits activation of nuclear factor kappa B in human T cells. *Free Radical Biology Medicine* 2, 345-350.
16. Uchida, Y., Yakahashi, T.: (1975) The characteristic of antibacterial activity of garlic. *Japanese Journal of Antibiotics* 28, 638-642.
17. Bhowmik, A., Seemungal, T. A. R., Sapsford, R.J. 2000. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 55: 114-120
18. Krest, I., Keusgen, M. : (1999) Quality of herbal remedies from *Allium sativum* Difference between alliinase from garlic powder and fresh garlic. *Planta Medica* 65 (2), 1139-1143.
19. Hodge, G., Hodge, S., Hang, P. 2002. Garlic suppresses leukocyte inflammatory cytokine production in vitro; potential therapeutic use in inflammatory diseases. *Cytometry* 48: 209-215
20. Testing of pulmonary functions – Text book of Essentials of respiratory functions 8<sup>th</sup> chapter, 183-190. American Thoracic Society/European Respiratory Society Task Force: Standardization of spirometry. *Eur Resp J*. 26: 2005; 319-338
21. American thoracic Society (1995) Standardization of spirometry, 1994 update. *Am J Repir Crit Care Med* 152: 1107- 1136.