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Original Article

Clinical efficacy of Bambuterol alone and in combination with Borage & Echium seed oil in chronic persistent asthma

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ABSTRACT

Introduction: Asthma chronic inflammatory disease, highly prevalent all ages, characterizes by cough, dyspnea, chest tightness, wheezing & impairment in physical activities. Inflammatory cells degranulation, release of numbers of mediators and toxic substances, leukotriene's are consider important. Bambuterol, reducing the frequency of recurrent episodes of bronchospasm and Borage & Echium seed oil, inhibits the leukotriene's generation & competing with the arachidonic acid, thus decreasing the inflammatory process.
Objective: To evaluate the clinical efficacy of Bambuterol alone and in combination with Borage & Echium seed oil in chronic persistent asthma.
Method & Materials: An interventional study, approved by BASR University of Karachi. Group-A, Bambuterol oral once daily & Group B, Bambuterol once daily & Borage seed oil 1.3 gram daily plus Echium seed oil 500mg twice daily for 90 days. Diagnosed 120-registered patients, 60 patients in each group completed study period, results compared by Spirometry, PEFR, daily symptoms diary card and clinical questionnaires evaluated statistically.
Results: Group-A at day-90, percentage change of FEV_1 4.7%, FVC 5.9%, PEFR 7.1%. Group-B, FEV_1 13.3%, FVC 9.2%, PEFR 15.2%, results are statistically highly significant. Symptoms improvement and reduction in night sleep awakening, decreased need of recue medicine. Drug safety was determined by observing reported adverse effects on serum level of Alkaline Phosphatase, SGPT, Cholesterol, HDL, LDL and compliance of drug was checked by follow up at day-30, 60 & 90 and in between daily symptom dairy card.
Conclusion: Improvement reported by mean of, reduced severity, improved clinical symptoms & quality of life and no serious adverse effects, results are highly significant. Combination therapy provided synergistic effect.

Key words: Asthma, Bambuterol, Borage/Echium seed oil, Spirometry, PEFR, Questionnaire

INTRODUCTION

It is currently observed, that asthma is at large in prevalence and severity, prevalence ratio is 10-20% in different countries populations, which represent an estimated 300 million cases across the globe [1]. Rapid expansion in Asian population, the prevalence is expected to increase, in response to occupational hazards and environmental pollution [2]. In Pakistan, asthma is major health issue with a prevalence of 5% [3]. Numbers of inflammatory cells degranulation's, release of series of chemical mediators and toxic substances claim to be important, in the pathophysiology of the asthma, of which leukotrienes derived from arachidonic acid exist in a variety of isoforms, importantly Cysteinyl leukotriene's, (LTC_4, D_4 & E_4) are considered to play leading role [4].
The important factor in asthma is inflammation and edema, usually IgE-mediated, and release of

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chemical mediators like histamine, prostaglandin, and most importantly leukotriene's [5]. Studies of Lam [6], in broncho-alveolar lavage (BAL), Creticos [7], in urine collections, exclusively after allergen challenge, and Chu [8], detected increased production of Cysteinyl leukotriene's, during an acute asthma attack.

The diversity of mediators involved in asthma is unlikely, targeting a single cytokine/chemokine, to provide significant and persistent clinical benefit. However inflammatory components, have significant contribution in health and disease [9]. Earlier mostly medicinal products were extracted from natural sources, proven scientifically non-toxic, health benefit component, used in prevention and treatment [10]. Botanical oils, as a source of ω-3 and ω-6 fatty acids, developed an enormous interest in research to prevent the incidences of inflammatory diseases [11]. Dietary supplementation with Borage and Echium seed oil provides favorable opportunity, by modifying the metabolism of fatty acid and thus balance the pro-inflammatory mediators [12].

Borage seed oil is derived from the *Borago officinalis*, contain 17–28%, of plant-based source of fatty acid [13], of medicinal value in human diets, helpful in the treatment of a vast range of disorders [14]. *Echium plantagineum* seeds contain sufficient amounts of γ-linolenic acid, α-linolenic acid, and stearidonic acid lipids [15]. γ-linolenic acid is a product of the Δ^6 desaturase, obtaining dietary GLA bypasses the Δ^6-desaturase regulatory step, while humans have very little Δ^6-desaturase activity, (GLA) is elongated to DGLA, and then converted to arachidonic acid by Δ^5-desaturase. DGLA (Dihomo-γ-linolenic acid) released can be metabolized to 15-lipoxygenase product, 15-hydroxytrienoic acid, and virtually complete inhibition of leukotriene B_4 biosynthesis [16].

The hypothesis regarding the combination of Echium and Borage seed oils as sources of Stearidonic acid & γ-linolenic acid will inhibit leukotriene's generation without the side effect of increasing circulating arachidonic acid [17]. Bambuterol, oral β_2-adrenergic agonist with high metabolic stability is a pro-drug of terbutaline, show significant relief and apparently a complementary-enhancing advantage, is providing improved overall clinical results [18].

METHODS & MATARIALS

This Open label randomized clinical trial, were carried out in the Department of Pharmacology, BMSI, JPMC, in support with the Institute of Eastern Medicine, Hamdard University, and approved by BASR, University of Karachi.

Diagnosed chronic asthmatic patients of either sex were registered after consent, applied inclusion and exclusion criteria and confirmation of reversibility, by measuring at least 12% increase in FEV_1 after 15 minutes with an inhalation of 200 microgram (µg) Salbutamol [19].

Diagnosed 120 chronic persistent asthma patients divided into groups, completed the study period of 90-days. Group-A: were treated by Bambuterol 10 mg once daily orally at bed time for 90 days
Group-B: were treated with combination of Bambuterol 10 mg once at bed time & Borage 1.3 gram once plus Echium seed oil 500 mg twice daily orally for 90 days.
Each group patients after detail examination and data enter in the design pro forma, and record FEV_1, FVC by Spirometry & PEFR by peak flow meter and provided daily diary card to mark symptoms and measures, clinical respiratory questionnaire for compliance of the drugs and collection of blood sample for safety analysis.

All parameters of study were collected on the day of registration and patients were directed to report on day-30, 60 & day-90 with all parameter repeated for the final statistical evaluation of results from day-0 to day-90.

OBSERVATIONS/RESULTS

Initially interviewed 140 patients of chronic persistent asthma, only 120-patients completed the study duration of 90-days while the remaining lost the follow up and not maintained daily diary card so dropped from the study but medical support provided when needed. Group-A patients, with baseline characteristics are, male 59 (98.3%) and 1 (1.7%) female, mean age of 56$\pm$ 5.6 ranging from 47 years to 68 years. 55 (91.7%) were smokers and 5 (8.3%) were non-smokers, 42 (70%) of moderate severity and 18 (30.0%) were of severe rank of asthma classification. Baseline pulmonary data of, FEV_1 mean 1.25±0.19, FVC 2.4$\pm$0.4 and PEFR 195.8$\pm$39.5, Group-B patients with baseline characteristics 58 (96.7%) male & 2 (3.3%) female mean age 56.4$\pm$6.3 ranging from 42 years to 70 years. 53 (88.3.7%) smoker and 7 (11.7%) non-smokers, 47 (78.3%) of moderate severity and 13 (21.7%) of severe class of asthma severity. Baseline data of FEV1 mean 1.3$\pm$0.3, FVC 2.3$\pm$0.4 and PEFR 187.8$\pm$46.2 shown in Table-1.

Two groups, with different mechanism of action, comparing the FEV_1, FVC and PEFR in two different groups, Bambuterol treated group-A,

FEV_1 mean 1.31±0.18 (L) percentage change of 4.7%, FVC changes mean 2.5±0.3 percentage increase of 5.9%, PEFR mean 209.7±37.3 (L/mins) percentage change of 7.1% at day-90. Combination drug treated group-B, FEV1 was mean 1.5±0.3 with the percentage increase of 13.3%, FVC mean 2.5±0.4 with the percentage increase of 9.2%, and PEFR mean 215.8±50.3, with the percentage change of 15.2% results are highly significant at day-90.

Compared the pulmonary symptoms of diary card of two groups, (Cough, Dyspnea, Sputum production & Sleep disturbances) improved at day-90. Clinical Questionnaires of both groups exhibit effectiveness and better compliance, need of rescue medication (Short acting β_2 –adrenergic agonist) in group-A reduced to 15.0%, group-B reduced to 18.3% at day-90.

DISCUSSION

Bronchial asthma, increasing in prevalence and severity, clinically characterized by coughing, wheezing, & breathlessness, the majority of patients experience sleep disturbance and change in quality of life. There are many known toxic substances released by degranulation of inflammatory cells, particular importance are the leukotreine's, derived from arachidonic acid. Important factors that contribute or increase the incidence of asthma include environmental pollution, low birth weight, tobacco smoking, diet & viral infections.

Primary objectives to maintain normal (near normal) lung function. Documentation of FEV_1, FVC and PEFR, daily symptoms diary card, respiratory questionnaires and use of recue medications are most appropriate approach in the diagnosis & treatment of asthma. Pharmacological access in the therapy of asthma is to prevent or control asthma symptoms or at least to reduce the frequency and severity of acute exacerbations.

Chronic asthma management, number of combinations used to prevent or control the symptoms, few of them shows improvement in selected cases but the problem of toxicities, limits its long term use. In our research study, the efficacy and safety profile of drugs were determined.

Fugleholm, mentioned that Bambuterol strongly contributes to its 24-h duration of action and has similar clinical efficacy to other oral bronchodilators, but with less side effects, especially with regard to tremors [20]. A study compared pulmonary function & PEFR of Bambuterol with Montelukast, results showed improvement in asthma symptoms, pulmonary functions, Bambuterol showed more significant improvement in pulmonary function values compared to Montelukast [21].

In contrast, treatment with 10 mg Bambuterol did not show a statistically significant difference versus placebo as measured by FEV_1 24 hour after administration, but reported improvement in FEV_1, FVC & PEFR with continuous therapy during the study [22]. One comparative study, oral Bambuterol once-daily dose provides a highly effective alternative to twice-daily inhaled Salmeterol for relief of nocturnal symptoms in moderate to severe asthma patients [23].

Improvements in features of chronic persistent asthma have shown significant result for FEV_1 with FVC & PEFR numerically in favor of combination therapy. Symptom evaluation by daily dairy card and clinical questionnaire in both groups showed improvement and reduction in night sleep awakening decreased need of recue medicine during the 90 day period of study. Compliance was excellent in both groups as all patients used the drugs prescribed as explained to them.

Echium & Borage seed oil containing a dangerous chemical, pyrrolizidine alkaloids, are hepatotoxic [24]**.** Adverse reactions were reported in 18 out of 60 patients of Bambuterol group and in Group-B 25 out of 60 patients. As regards the drug safety & adverse effects in both groups did not show a major numerical shift towards any group, however in combination group lipid profiles exhibited more beneficial effects than the bambuterol alone group.

CONCLUSIONS

The worldwide prevalence of asthma is increasing, management approach differs according to location, traditions, and availability of resources and medications, but the common ambitions are to reduce asthma morbidity and mortality. The present study has several strong points. The data were derived from a sample of the general adult population. The combination therapy of group-C (Bambuterol and addition of Cap Borage seed oil 1.3 gram plus Echium seed oil 500mg) showed more effective and less adverse effects than other study group (Group-A) treated patients in chronic persistent asthma. In view of the clinical results, these findings mark toward prophylactic role of plant seed oil supplementation (Borage & Echium) in asthma.

Nutritional scientists, applied the knowledge to investigate the association between nutrients and chronic disease and reduces the incidence and

mortality, based on current hypotheses, about the role of dietary factors, PUFAs in disease control and prevention. In combination therapy of Group-B, revealed the advantage in improving the pulmonary functions and symptoms, by acting two different mechanisms, so the combination provide a synergistic effect with minimum toxicities.

RECOMMENDATIONS/SUGGESTIONS

Thus, the possibility exists for drug–diet combination that confers greater benefits of chronic persistent asthma, than either intervention alone, or combination provide improvement in the quality of life with less toxicity. Multi-centric studies may be conducted in future for treatment regimens that are clinically efficacious and are safe for use in chronic persistent asthmatic patients.

TABLE-1: Baseline characteristics of Group-A & Group-B

	GROUP-A n=60	**GROUP-B n=60**	**p-value**
Gender			
Female	1 (1.7%)	2 (3.3%)	0.814
Male	59 (98.3%)	58 (96.7%)	
Age in years (Mean±SD)	56.9±5.6	56.4±6.3	0.025
Smokers	55 (91.7%)	53 (88.3%)	0.23
Non-Smokers	5 (8.3%)	7 (11.7%)	
Severity			
Moderate	42 (70.0%)	47 (78.3%)	0.496
Severe	18 (30.0%)	13 (21.7%)	
FEV_1 Baseline	1.25±0.19	1.3±0.3	0.451
FVC Baseline	2.4±0.4	2.3±0.4	0.304
PEFR Baseline	195.8±39.5	187.3±46.2	0.075

Group-A: Tab Bambuterol 10 mg once daily; **Group-B:** Combination of Tab Bambuterol 10 mg daily & Tab Borage 1.3 gram once plus Echium seed oil 500 mg twice daily; **n-**: Number of Patients; **FEV_1**: Forced expiratory volume in 1-second; **FVC**: Forced vital capacity; **PEFR**: Peak expiratory flow rate

TABLE-2: Comparison of FEV1, FVC & PEFR between Group-A & Group-B.

GROUPS	Tab Bambuterol Group-A (n=60)	Tab Bambuterol & Cap Borage plus Echium seed oil Group-B (n=60)	p-value
FEV1			
Day-0	1.25±0.19	1.3±0.3	0.436
Day-90	1.31±0.18	1.5±0.3	0.001
Total percentage change	4.7%	13.3%	
FVC			
Day-0	2.4±0.4	2.3±0.4	0.274
Day-90	2.5±0.3	2.5±0.4	0.958
Total percentage change	5.9%	9.2%	
PEFR			
Day-0	195.8±39.5	187.3±46.2	0.281
Day-90	209.7±37.3	215.8±50.3	0.447
Total percentage change	7.1%	15.2%	

TABLE-3: Comparison of Clinical Questionnaire, Group-A & Group-B

Assessment of drug effectiveness and compliance of patients	GROUP-A	GROUP-B
Is cough worse than previously D-0	11 (18.3%)	8 (13.3%)
Is cough worse than previously D-90	3 (5.0%)	0 (0.0%)
Is Dyspnea worse than previously D-0	13 (21.7%)	7 (11.7%)
Is Dyspnea worse than previously D-90	3 (5.0%)	0 (0.0%)
Is there increase in sputum production D-0	7 (11.7%)	7 (11.7%)
Is there increase in sputum production D-90	0 (0.0%)	5 (8.3%)
Is sleep is more disturbed than previously D-0	7 (11.7%)	9 (15.0%)
Is sleep is more disturbed than previously D-90	3 (5.0%)	4 (6.7%)
Sleep Awakening D-0	60 (100.0%)	60(100%)
Sleep Awakening D-90	15 (38.3%)	25 (41.7%)
Is there any need to rescue medications D-0	60 (100.0%)	60 (100.0%)
Is there any need to rescue medications D-90	9(15.0%)	11(18.3%)

TABLE-4: Comparison of adverse drug reactions of Group-A & Group-B

	GROUP-A	GROUP-B
BITTER TASTE	0(0.0%)	1(1.7%)
VOMITING	0(0.0%)	2(3.3%)
ANOREXIA	4(6.7%)	4(6.7%)
HEMOTURIA	0(0.0%)	1(1.7%)
SEIZURES	0(0.0%)	0(0.0%)
FATIGUE	5(8.3%)	4(6.7%)
PALPITATION	2(3.3%)	4(6.7%)
HEADACHE	1(1.7%)	4(6.7%)
TREMERS	2(3.3%)	2(3.3%)
MUSCLE CRAMPS	4(6.7%)	2(3.3%)
HYPERSENSITIVITY	0(0.0%)	1(1.7%)

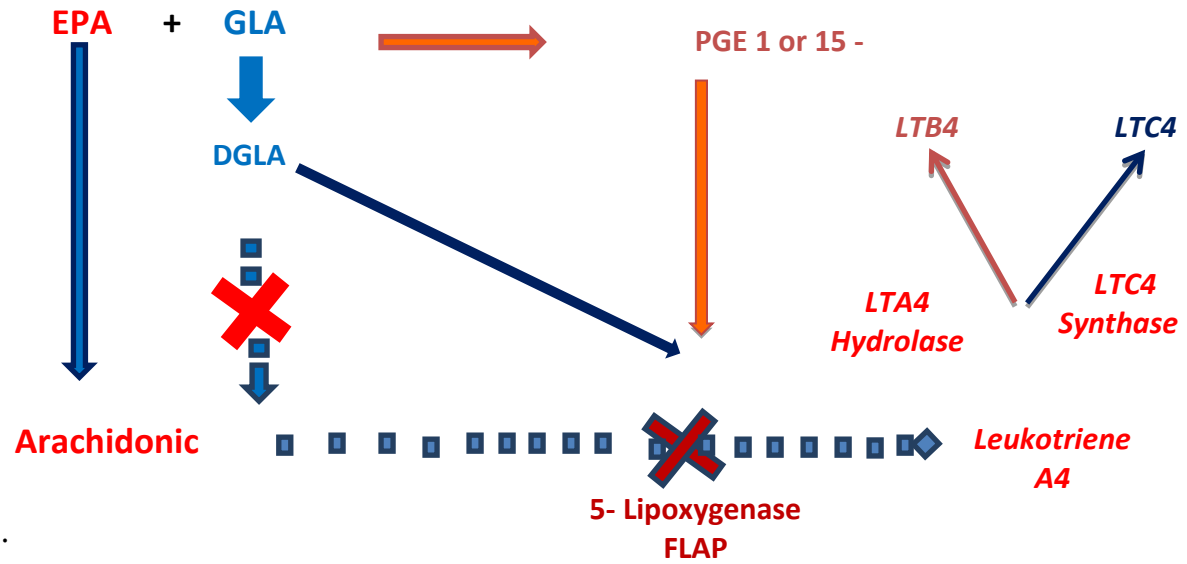
TABLE-5: Drug safety - Hepatic & lipid profile

Blood parameters	DAY-0	DAY-90	p-value
GROUP-A			
Alkaline Phosphatase U/L	144.6±18.2	143.5±17.5	0.354
SGPT U/L	30.3±5.3	31.3±4.5	0.023
Cholesterol mg/dl	205.3±31.5	207.2±32.2	0.014
HDL mg/dl	31.5±6.2	31.7±6.1	0.811
LDL mg/dl	137.1±18.8	139.6±18.8	0.001
GROUP-B			
Alkaline Phosphatase U/L	139.2±19.3	143.6±16.7	<0.0001
SGPT U/L	31.0±4.5	32.7±4.3	<0.0001
Cholesterol mg/dl	189.7±27.4	171.5±24.0	<0.0001
HDL mg/dl	29.7±5.9	36.4±5.5	<0.0001
LDL mg/dl	160.6±22.9	148.8±21.6	<0.0001

FIGURE-1

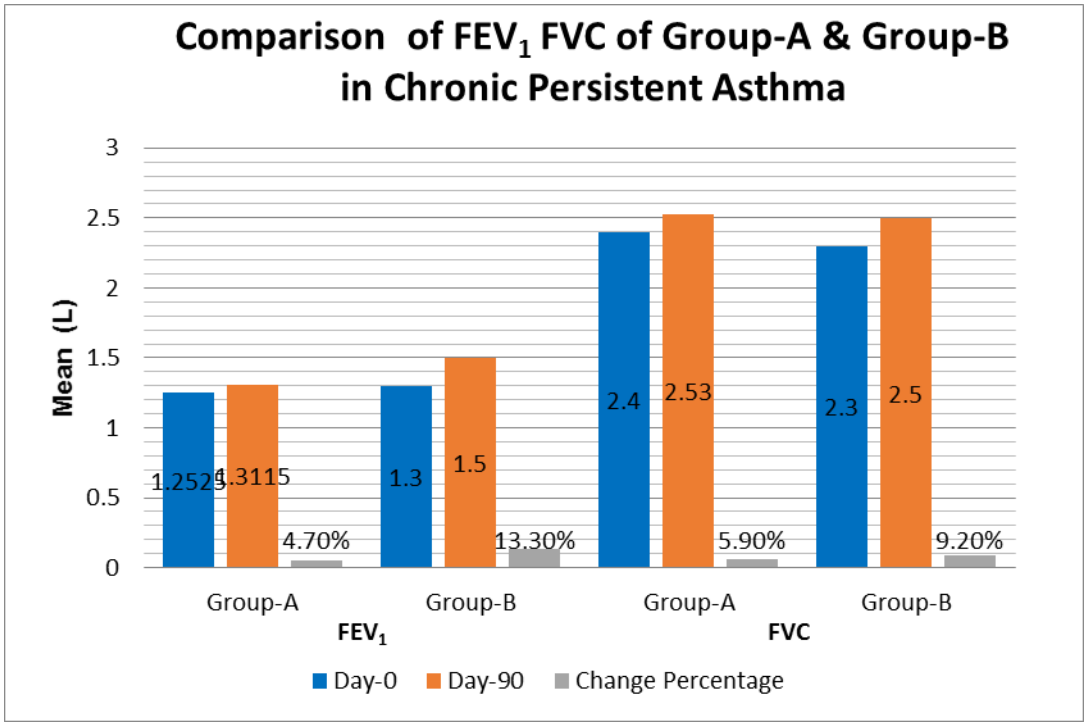
Potential mechanism by which Eicosapentaenoic acid (EPA) and γ-linolenic acid (GLA), inhibits lipid mediator production.

Lipid mediators are PGE1, 15-HETre, DGLA, LT, FLAP.



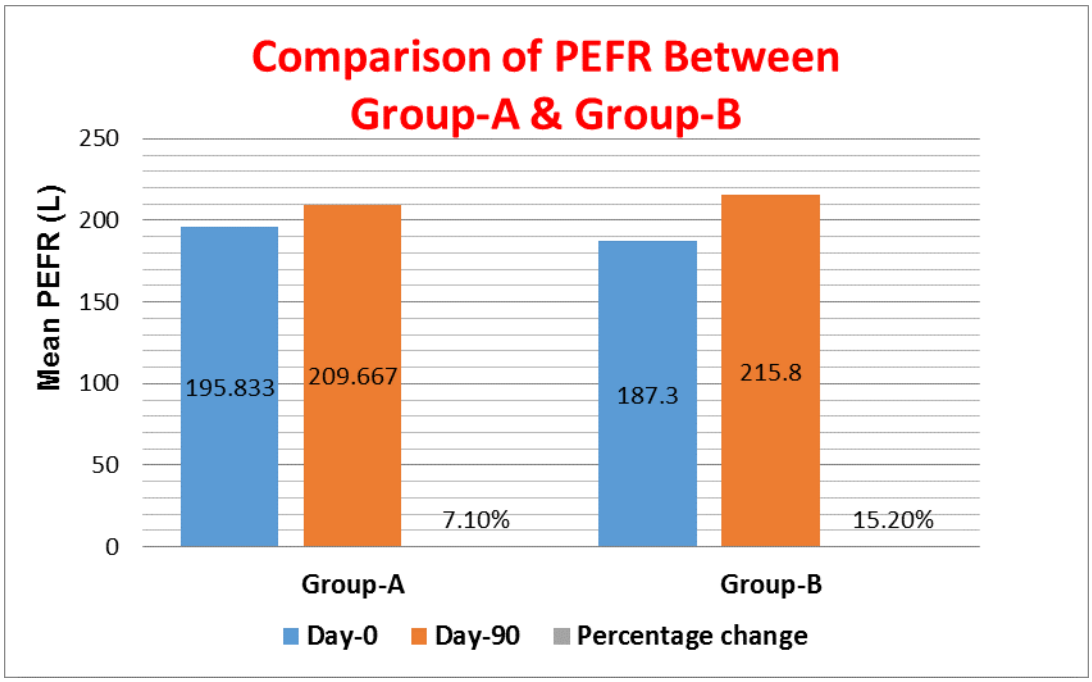
(Adopted from Chilton, 2008)

Figure-2



Group-A: Bambuterol treated patients of chronic persistent asthma
Group-B: Combination (Bambuterol & Borage plus Echium seed oil) treated patients.

Figure-3



Group-A: Bambuterol treated patients of chronic persistent asthma
Group-B: Combination (Bambuterol & Borage plus Echium seed oil) treated patients.

REFRENCES:

1. Mannino DM et al. Surveillance of asthma-US 1980-1999. MMWR. 2002; 51(SS01):1-13.
2. de Nijs SB et al. Adult-onset asthma: is it really different? Eur Respir Rev 2013; 22:44-52.
3. Datta A. News report. The News International 2007.
4. Montuschi P. Role of Leukotriene's and Leukotriene Modifiers in Asthma (Review) Pharmaceuticals. 2010; 3:1792-1811
5. Galli SJ et al. Mast cells are tunable effector and immune-regulatory cells: resent advances. Ann Rev Immunol. 2005; 23:749-86
6. Lam S et al. Release of leukotriene's in patients with bronchial asthma. J Allergy Clin Immunol. 1988; 81:711-7.
7. Creticos PS et al. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. N Engl J Med. 1984; 310:1626-30.
8. Chu SJ et al. In situ amplification of Five- lipoxygenase and 5-lipoxygenase-activating protein in allergic airway inflammation & inhibition by leukotriene blockade. J Immunol. 2000; 165: 4640-8.
9. Busse WW, Karaft M. Cysteinyl leukotrienes in allergic inflammation: Strategic target for therapy. Chest. 2005; 127: 1312–1326.
10. Pieszak M et al. Borage: a valuable medicinal plant used in herbal medicine. Herba Polonica. 2012; 58:95-103.
11. Chilton FH et al. Mechanisms by which botanical lipids affect inflammatory disorders. Am J Clin Nutr. 2008. 87(2):.498S-503S.
12. Miles EA et al. The influence of different combinations of gamma-linolenic acid, stearidonic acid and EPA on immune function in healthy young male subjects. Br J Nutr.2004; 91(6):893-903.
13. Eskin NAM. Borage and evening primrose seed oil. Eur J Lipid Sci. Technol. 2008; 110: 655–661.
14. Gupta M, Singh S. *Borago officinalis* Linn. An important medicinal plant of Mediterranean region: a review. Int J Pharm Sci Res. 2010; 5: 27-34
15. Abedi E, Sahari MA. Long-chain polyunsaturated fatty acid sources and evaluation of their nutritional and functional properties (Review) Food Science & Nutrition. 2014; 2(5): 443– 463.
16. Chilton L et al. Metabolism of gamma linolenic acid in human neutrophils. J Immunol.1996; 156: 2941–7.

17. Arm JP et al. Impact of botanical oils on polyunsaturated fatty acid metabolism and Leukotriene's generation in mild asthmatics. Lipids Health Dis. 2013; 2 (12):141.
18. Cazzola M et al. Novel bronchodilators in asthma. Curr Opin Pulm Med. 2010; 16(1): 6-12.
19. Global Initiative for Chronic Obstructive Lung Disease (GOLD) updated 2014
20. Fugleholm AM et al. Therapeutic equivalence between bambuterol, 10 mg once daily, and terbutaline controlled release, 5 mg twice daily, in mild to moderate asthma. Eur Respir J. 1993; 6(10): 1474–1478.
21. Ahmed MAl. Bambuterol versus Montelukast in patients with chronic asthma. Asian Journal of Pharmacy, Nursing and Medical Sciences. 2015; 3 (1): 8-12.
22. Persson G et al. One month treatment with the once daily oral beta-2 agonist (Bambuterol) in asthmatic patients. Euro Respir J. 1995; 8: 34-39
23. Wallert B et al. Comparison of two long acting β-agonist, oral Bambuterol and inhaled salmeterol, in the treatment of moderate to severe asthmatic patients with nocturnal symptoms. Respir Med. 1999;93: 33-38
24. Cheeke PR. Toxicity and metabolism of pyrrolizidine alkaloids. Journal of Animal Science. 1988. 66; 2343-2350