



CHRONIC PERSISTENT ASTHMA; IMPACT OF BOTANICAL SEED OILS (BORAGE & ECHIUM) VERSUS COMBINATION WITH BAMBUTEROL ON THE SEVERITY OF CHRONIC PERSISTENT ASTHMA

Syed Saud Hasan¹, Moosa Khan², Musarrat Sultana³, Muhammad Talha Farooqui⁴, Asif Iqbal⁵

1. PhD
Department of Pharmacology,
Dow Medical College
Dow University of Health Sciences,
Karachi.
2. PhD
Professor,
Department of Pharmacology
Pakistan Institute of Medical
Sciences, Islamabad.
3. DMJ
Associate Professor
Department of Forensic Medicine
Dow International Medical College
DUHS, Karachi.
4. MD
University of Nevada School of
Medicine
Las Vegas USA.
5. PhD
Chairman Eastern Medicine
Hamdard Medical University,
Karachi.

Correspondence Address:
Prof Dr. Syed Saud Hasan
Department of Pharmacology, DMC
Dow university of Health Sciences,
Karachi.
saudhz@hotmail.com

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INTRODUCTION

Asthma prevalence in different countries populations is 10-20%, which represent an estimated 300 million cases across the globe.¹ In Asia with overall perception comes to <5%, may be passed over from childhood to newly developed disorder in response to occupational hazards and environmental pollution.²

The population of the Asia in recent decade has increased four folds, asthma has been recognized as major chronic disease.^{3,4} In Pakistan asthma is a major health issue with a prevalence of 5%.⁵

Classification based on FEV₁ post-bronchodilator

ABSTRACT... Asthma, a chronic inflammatory disorder, prevalence is high in all ages, characterizes by cough, dyspnea, chest compression, wheezing and considerable impairment in physical activities. **Study Design:** An interventional study. **Objectives:** Observe improvement in pulmonary functions, symptoms & quality of daily life with safety profile in chronic moderate persistent asthma. **Place & Duration:** Approved with BASR University of Karachi and conducted with the participation BMSI (Pharmacology), JPMC & Eastern Medicine HMU, Karachi. **Method & Materials:** Total 120 diagnosed with objective signs of reversibility, by measuring at least 12% increase in FEV₁ after 15 minutes with an inhalation of 200 microgram (μ g) Salbutamol of asthmatic patients were registered & divided in two groups. Group-A treated with oral Borage 1.3 gram once plus Echium seed oil 500mg twice daily & Group B treated with Borage 1.3 gram once plus Echium seed oil 500mg twice along with oral Bambuterol 10mg once daily for 90 days, results of Spirometry, PEFR, daily dairy symptoms card and clinical questionnaire were statistically evaluated, to estimate the improvement and compliance of the drugs. **Results:** Borage & Echium treated groups from baseline to day-90, FEV₁ mean 1.30+0.02 (L) change of 4.7%, FVC mean 2.3+0.3 increase of 2.19%, PEFR mean 186.3+34.1 (L/mints) change 4.1%. In group-B, FEV₁ mean 1.5+0.3 increase of 13.3%, FVC mean 2.5+0.4 increase of 9.2%, PEFR mean 215.8+50.3, change of 15.2%, results are highly significant. Symptoms of daily dairy card in both group shows improvement, and reduction in night sleep awakening and clinical questionnaire shows improved symptoms, decreased need of rescue medicine at day-90. **Conclusion:** Combination therapy, provided synergistic effect, to reduce the severity, improve symptoms, quality of life along with the safety profile, results are highly significant.

Key words: Borage/Echium Seed Oil, Bambuterol, Spirometry, PEFR, Daily Symptoms Diary Card, Respiratory Questionnaire.

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results, according to severity of flow of air limitation, in mild cases FEV₁ > 80% predicted, moderate cases <50% to < 80% predicted, severe cases <30% to < 50% predicted, in very severe cases FEV₁ < 30% predicted.⁶

In the etiology of asthma multiple factors are involved, usually IgE-mediated antigen-antibodies interaction and release of chemical mediators like histamine, prostaglandin, and most importantly leukotrienes, in addition, trigger factors like allergy, infections, hereditary, psychosocial and environmental factors, resulting in exacerbation that results in the severity of the disease.⁷ Numbers of chemical mediators and toxic substances

released by degranulation of inflammatory cells, cysteinyl-leukotrienes, (LTC_4 , LTD_4 & LTE_4) are considered to play dominant role.⁸

The diversity of mediators, which contribute to bronchospasm, therefore it's unlikely to obtain any significant and persistent clinical benefit by targeting a single cytokine/chemokine. Dietary adjustments may help the patients and manage asthma, as well as contribute to their overall health.

Dietary contents, polyunsaturated fatty acids (PUFAs) are widely accepted, but the type of consumed fat may be more important than the amount of fat intake, research on fatty acid has attracted on two main components of polyunsaturated fatty acids, that is intake of omega-3 and omega-6, while omega-3 fatty acids are considered essential to human health, but cannot be manufactured by the body.⁹

Earlier mostly medicinal products were extracted from natural sources, proven scientifically non-toxic, health benefit component in the prevention and treatment of disease.¹⁰ Borage seed oil is derived from the *Borago officinalis*, contain 17–28%, of a plant-based source of fatty acid.¹¹ Borage seed oil has medicinal value in human diets, helpful in the treatment of a vast range of inflammatory disorders.¹²

Echium plantagineum seeds contain sufficient amounts of γ -linolenic acid, α -linolenic acid, and stearidonic acid, a content of lipids.¹³

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.¹⁴ Figure-1

Bambuterol, oral β_2 -long acting agonist, a pro-drug of terbutaline used once-daily, as a bronchodilator showed significant relief and providing improved overall clinical results.¹⁵

Purpose of Study

To evaluate the efficacy of Botanical seed oils

(Borage & Echium) & with combination of long acting β_2 agonist (Bambuterol) in improving asthma control, with efforts to suppress inflammation over long term & safety profile in chronic persistent asthmatic patients.

METHODS & MATERIALS

This open-label randomized clinical trial conducted in the Department of Pharmacology, Basic Medical Sciences Institute, Jinnah Post-graduate Medical Centre Karachi after the approval of BASR University of Karachi & Ethical Committee of the Institute. Diagnosed patients of either sex were registered after confirming signs of reversing, by measuring FEV_1 increases at least 12% after 15 minutes with an inhalation of salbutamol 200 μ g.⁶ Registered 120 patients, 60 each in group A & B.

“All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (International and National) and with the Helsinki declaration of 1975, as revised in 2008. Informed consent was obtained from all subjects for being included in the study”

Group-A: Treated with oral Borage 1.3 gm once plus Echium 500 mg twice daily for 90 days

Group-B: Combination therapy of oral Borage 1.3 gm once plus Echium seed oil 500mg twice daily & oral Bambuterol 10 mg once daily for 90 days.

Each group patients after detail history, physical and systemic examination, enter in the design proforma, record FEV_1 & FVC, & PEF, daily diary symptoms card, clinical respiratory questionnaire and blood sample collected for safety analysis. Patients are directed to report on Day-30, 60 and Day-90 and all parameters statistical interpretation at day-90.

The data were recorded and analyzed by using SPSS computer software version 21. Results were given in the text as mean and standard deviation for quantitative variables and percentage / proportion for qualitative variables like gender,

symptoms, adverse effect etc. An analysis of variance (ANOVA) was used for quantitative variables. P-value < 0.05 was considered as significant

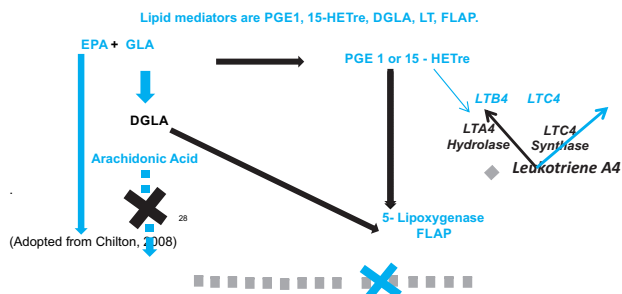


Figure-1. Potential mechanism by which Eicosapentaenoic acid (EPA) and gamma-linolenic acid (GLA), inhibits lipid mediator production.

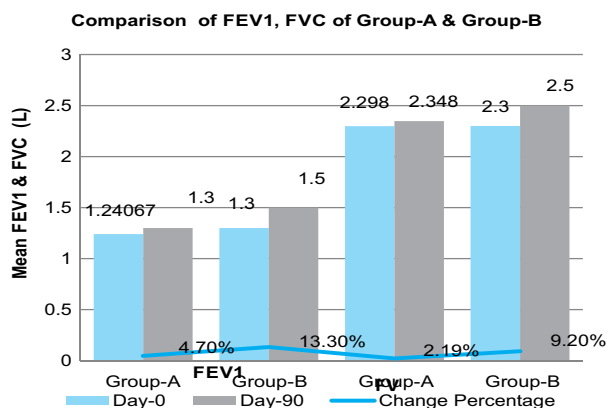


Figure-2. Group-A: Borage Plus Echium seed oil treated patients in chronic persistent asthma Group-B: Combination treatment of Borage plus Echium seed oil & Bambuterol in chronic moderate persistent asthma.

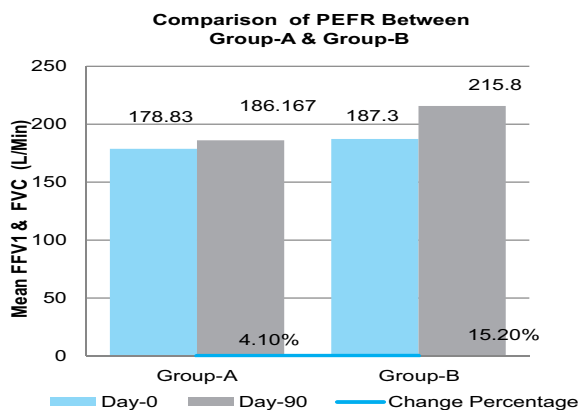


Figure-3. Group-A: Borage Plus Echium seed oil treated patients in chronic persistent asthma Group-B: Combination treatment of Borage plus Echium seed oil & Bambuterolin chronic moderate persistent asthma.

RESULTS

Earlier 140-patients registered for the study of either sex, placed in the divided groups A & B.

Patients of either group are encouraged to make sure, follow the instruction provided and keep records of daily symptoms & PEFR before going to sleep and maintain daily diary card till the next follow-up and report to the center from where he/she is registered.

On follow-up day, always with daily diary card for evaluation of symptoms and further review of pulmonary functions and collection of blood samples for liver function test & Lipid profile for the drug safety determination.

During the study, twenty patients were dropped because of irregularity in drug intake and follow-up failure, not maintain the daily diary card, but medical support continues when needed.

Group-A registered sixty patients completed study duration of 90-days treatment, with the following baseline characteristics are, male 58 (96.7%) with the mean age of 59.4±7.5 (ranging from 45 years to 70 years). 58 (96.7%) were smokers, 42 (70%) of moderate severity and 18 (30.0%) were of a severe rank of asthma classification. Patients had baseline reading of FEV₁ mean 1.2±0.2, FVC 2.3±0.3 and PEFR 178.8±35.3. Table-I

Group-B, baseline characteristics are female 58 (96.7%) mean age 56.4±6.3 (ranging from 42 years to 70 years), 53 (88.3%) were smokers, having 47 (78.3%) of moderate severity and 13 (21.7%) of a severe class of asthma severity. Baseline, FEV₁ means 1.3±0.3, FVC 2.3±0.4 and PEFR 187.8±46.2.

Comparing the two study groups, at day-90, in a group-A change of mean FEV₁ 1.3±0.2, percentage increase 4.7%, FVC mean 2.3±0.3, percentage increase 2.19%, PEFR mean 186.2±34.1, with percentage change 4.1%. Group-B, FEV₁ mean 1.5±0.3, percentage increase 13.3%, FVC mean 2.5±0.4, percentage increase 9.2%, PEFR mean 215.8±50.3, with the percentage increase 15.2%, results are highly significant. Table-I Figure-2 & 3

	Group-A (n=60)	p-value	Group-B (n=60)	p-value
FEV1		<0.0001		<0.0001
Day-0	1.2±0.2		1.3±0.3	
Day-90	1.3±0.2		1.5±0.3	
Total percentage change	4.7%		13.3%	
FVC		<0.004		<0.0001
Day-0	2.3±0.3		2.3±0.4	
Day-90	2.3±0.3		2.5±0.4	
Total percentage change	2.19%		9.2%	
PEFR		<0.0001		<0.0001
Day-0	178.8±35.3		187.3±46.2	
Day-90	186.2±34.1		215.8±50.3	
Total percentage change	4.1%		15.2%	

Table-I. Comparison of FEV₁, FVC & PEFR between groups-A&B

Daily Dairy Card Symptoms	Group-A			Group-B		
	Day-0	Day-90	p-value	Day-0	Day-90	p-value
Dyspnea	2 (0)	1 (1)	<0.0001	2 (0)	1 (0)	<0.0001
Cough	2 (1)	1 (0)	<0.0001	2 (1)	1 (0)	<0.0001
Sputum Production	2 (0)	1 (1)	<0.0001	2 (1)	1 (1)	<0.0001
Night Sleep disturbances	2 (0)	1.5 (1)	<0.0001	1 (1)	1 (1)	<0.0001
Night Sleep Awakening	60 (100%)	38 (63.3%)	<0.0001	60 (100%)	25 (41.7%)	<0.0001
No of Exacerbation	2 (0)	2 (0)	0.157	0 (0)	2 (0)	<0.0001

Table-II. Comparison of symptoms score & exacerbations between group-A& group-B

Assessment of Drug Effectiveness and Compliance of Patients	Groups			
	A		B	
	Day-0	Day-90	Day-0	Day-90
Is cough worse than previously	8 (13.3%)	4 (6.7%)	8 (13.3%)	0 (0.0%)
Is Dyspnea worse than previously	12 (20.0%)	5 (8.3%)	7 (11.7%)	0 (0.0%)
Is there increase in sputum production	5 (8.3%)	3 (5.0%)	7 (11.7%)	5 (8.3%)
Is sleep is more disturbed than previously	12 (20.0%)	8 (13.3%)	9 (15.0%)	4 (6.7%)
Night Sleep Awakening	60 (100.0%)	21 (35.0%)	60 (100%)	25 (41.7%)
Is there any need to rescue medications	60 (100.0%)	25 (41.7%)	60 (100.0%)	11 (18.3%)

Table-III. Comparison of clinical questionnaires in group-A with group-B

Group-A Tab Borage 1.3 g once/Echium seed oil 500mg twice daily

Group-B Combination of Tab Bambuterol 10mg OD+ Tab Borage/Echium seed oil 500mg BD

n- Number of Patients

FEV₁- Forced expiratory volume in 1-second

FVC-Forced vital capacity

PEFR- Peak expiratory flow rate

Compared the two group's pulmonary daily diary card symptoms (Cough, Dyspnea, Sputum production, sleep disturbances) improved at day-90. Patients of group-B exhibit highly significant improvement in symptoms and reduction of the

number of exacerbation. Table-II

Group-A Tab Borage 1.3 g once daily/Echium seed oil 500mg twice daily

Group-B Combination of Tab Bambuterol 10mg once& Tab Borage 1.3 g once plus Echium seed oil 500mg twice daily.

Night sleep awakening in a group-A reduce from 100% to 35% and in the group-B decrease from 100% to 41.7% at day-90. The need of rescue medication (Short-acting β₂-adrenergic agonist) in group-A reduced from 100% to 47.1%, in group-B 100% to 18.3%. Table-III

Adverse Drug Effects	Group-A	Group-B
Bitter taste	0(0.0%)	1(1.7%)
Vomiting	1(1.7%)	2(3.3%)
Anorexia	1(1.7%)	4(6.7%)
Hematuria	0(0.0%)	1(1.7%)
Fatigue	0(0.0%)	4(6.7%)
Palpitation	2(3.3%)	4(6.7%)
Headache	2(3.3%)	4(6.7%)
Tremors	0(0.0%)	2(3.3%)
Muscle cramps	3(5.0%)	2(3.3%)
Hypersensitivity	0(0.0%)	1(1.7%)

Table-IV. Drug adverse effects in group-A & B patients.

Blood Parameters	Day-0	Day-90	p-value
Group—A			
Alkaline Phosphatase U/L	158.6±15.2	159.2±15.3	0.177
SGPT U/L	34.8±18.6	36.5±18.5	<0.0001
Cholesterol mg/dl	192.8±42.1	177.5±31.1	<0.0001
HDL mg/dl	28.6±6.0	34.2±5.8	<0.0001
LDL mg/dl	127.8±8.5	123.7±9.0	<0.0001
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

Table-V. Blood parameters analysis between group-A & group-B patients.

Group-A: Tab Borage 1.3 g once /Echium seed oil 500mg twice daily
 Group-B:Combination of Tab Bambuterol 10 mg daily & Cap Borage seed oil 1.3 g once plus Cap Echium seed oil 500 mg twice daily.

Safety Profile

Echium & Borage seed oil containing a dangerous chemical,pyrrolizidine alkaloids, are hepatotoxic.¹⁶ Adverse reactions were reported in group-A, 9 out of 60 patients and in Group-B, 25 out of 60 patients. Table-IV

Group-A, patient’s blood parameters of serum alkaline Phosphatase are all within the healthy limit, but SGPT level increased at day-90, statistically showed highly significant, but clinically within the normal healthy limit. Whereas Cholesterol decreases, HDL increases and LDL decrease at the completion of therapy, statistically highly significant.

In group-B patient’s blood parameters of serum alkaline Phosphatase & SGPT, are statistically highly significant, but clinically within normal limit, need close monitoring of treated patients, while Cholesterol, HDL, LDL are statistically highly significant, can safely be administered in chronic persistent asthma patients.Table-V

Group-A Tab Borage 1.3 g once/Echium seed oil 500mg twice daily
 Group-B Combination of Tab Bambuterol 10mg OD& Tab Borage 1.3 g Once daily/Echium seed oil 500mg twice daily
 SGPT-Serum glutamic-pyruvic transaminase
 HDL-High density lipoprotein
 LDL- Low density lipoprotein
 p-value< 0.05 significant

DISCUSSION

Asthma is characterized by hyper responsiveness to a variety of stimuli, and release many mediators & potentially toxic substances by degranulation

of eosinophils, basophils & mast cells. In recent years, factors demonstrated are genetic factors, mediators, growth factors, and leukotrienes.¹⁷

Asthma management and control, the primary objectives are to maintain normal lung functions (near normal). A drug-diet approach, in reducing the frequency and the severity of acute exacerbation or at least control the symptoms. The number of combinations used to prevent or control the symptoms, few of them shown improvement in selected cases, but the problem of toxicities limits its long term use.

Our research study, the efficacy, and safety profile of botanical seed oils (Borage & Echium), a rich source of ω -3 & ω -6 and the combination of Bambuterol and Borage plus Echium seed oil were studied. The primary objective in asthmatic patients was to determine the influence of Borage & Echium seed oil on metabolism and generation of leukotrienes.

Borage & Echium seed oil supplementation increases, circulating levels of three polyunsaturated fatty acids, i.e. Dihomo- γ -linolenic acid, Eicosapentaenoic acid and Docosahexaenoic Acid. GLA found in both Borage and Echium seed oil, in cells and tissues, gamma linolenic acid is readily elongated to Dihomo- γ -linolenic acid, once formed, is incorporated into inflammatory cells and tissues and competes with arachidonic acid.

Human mononuclear leukocytes, additionally convert Dihomo- γ -linolenic acid to a 15-lipoxygenase product, 15-hydroxyeicosatrienoic acid (15-HeTrE), which showed potent blocker of LTB_4 formation.¹⁸

Study of Perilla seed oil, one of the highest proportion 54-64% ω -3 fatty acids, & 14% ω -6 fatty acid, established significant differences observed after 4 weeks of dietary supplementation, in the value of FVC ($p < 0.05$) and FEV_1 ($p < 0.05$), suggest useful, with administration of ω -6 & ω -3 for the treatment of asthma in terms of suppression of LTB_4 and a generation of LTC_4 and improvement of pulmonary functions.¹⁹

Daily one gram administration of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in a double-blind study in 12 asthmatic subjects, 23% increase in forced air volume was observed after 9 months therapy.²⁰

Echium and Borage seed oils exhibited a good outcome by changing the inflammatory process.²¹

A related study also demonstrated an improved asthma-related quality of life following supplementation of EPA & GLA.²²

In one study showed, dietary intake of low ω -3 fatty acid is resulted in decreased pulmonary function and increased respiratory symptoms.²³

Nagakura found that intake of 120 mg of ω -3 (PUFAs) daily for 10-months compared with controls, reduces asthma symptoms score and bronchial hyper reactivity.²⁴

In another placebo-controlled study with moderate persistent asthma, six weeks of food supplementation with 1 gram of triglyceride oil (containing 30% EPA/DHA) resulted in a significant improvement of lung functions.²⁵

To our knowledge, this is the first study that compared the efficacy and safety with the combination of Borage & Echium seed oils & Bambuterol therapy, showed synergistic effects, compared with Bambuterol treatment only, pulmonary function and quality of life improvement significantly with no notable toxicity during the study period.

In this combination therapy showed the advantage by improving the pulmonary functions and symptoms, through two different mechanisms, Borage & Echium seed oil inhibits the leukotriene's generation as well as competing with the arachidonic acid, thus decreasing the inflammatory process, and Bambuterol activate the β_2 -receptors in the lung, reducing the frequency of recurrent episodes of bronchospasm.

A related study describes, that Bambuterol

showed similar clinical efficacy to other oral bronchodilators to its 24-hrs duration of action, but with fewer side effects, especially with regard to tremors.²⁶

A study compares, pulmonary function test & PEFR of Bambuterol with Montelukast, revealed improvement in asthma symptoms, pulmonary function values, more significant improvement in pulmonary function showed in Bambuterol compared to Montelukast.²⁷

CONCLUSIONS

The worldwide prevalence of asthma is increasing, but the common ambitions are to reduce asthma morbidity and mortality. The dietary addition of the medicinal foods, like Borage seed oil along with Echium seed oil to asthma management regimens, can improve health-related quality of life (HRQoL) of patient's and can also improve asthma control, evidenced by improving pulmonary functions, reduced asthma symptoms.

The present study showed active impression that the data derived from a sample of the general adult population, an opportunity for beneficial interaction effects with seed oil supplementation and Bambuterol.

Thus, the possibility exists for drug-diet combination that confers greater benefits of chronic persistent asthma, than either intervention alone, or combination provide an improvement in the quality of life with less toxicity.

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

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Syed Saud Hasan	Original Author (Study design)	
2	Moosa Khan	Supervisor of the project and review & correction as needed.	
3	Musarrat Sultana	Literature search, grammar check, organization and tabulation.	
4	M. Talha Farooqui	Provide compounds and Article reference from Hospital Library, Literature search.	
5	Asif Iqbal	Arrange and label patients and help in the collection of data in the design proforma.	