An herbal blend of *Boswellia serrata* and *Aegle marmelos*, with and without *Glycyrrhiza glabra*, improves functional respiratory outcomes and indices of well-being.

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INTRODUCTION

The gum resin extract of Indian frankincense (*Boswellia serrata)* is widely known for its anti-inflammatory properties, principally via inhibition of 5-lipoxygenase (5-LOX) (1). *Aegle marmelos*, also known as Bengal quince fruit, grows indigenously throughout India and is used extensively in Ayurvedic medicine as well as eaten in the diet (2). LI3109F, a novel composition comprised of a 1:1 ratio of the extracts of *B. serrata* gum resin and *A. marmelos* fruit, has previously been shown to inhibit leukotriene-dependent airway inflammation in animals as well as improve lung function, respiratory symptoms, and quality of life markers in asthmatic adults (3). Components of licorice root (*Glycyrrhiza glabra*), a plant native to the Mediterranean, may also impact respiratory function through anti-inflammatory pathways (4).

Daily exposure to air pollution can affect lung, cardiovascular, metabolic, and brain health of healthy people. Air pollutants and ambient small particulate matter exert their adverse effects by promoting oxidative stress and inducing inflammatory responses, specifically dysregulating type I helper T lymphocyte (Th1) and type II helper T-cell (Th2) immune responses (5,6). It remains unknown if supplementation with LI3109F or a combination of LI3109F and licorice root extract can promote better respiratory function and Th1/Th2 balance in healthy people who are frequently exposed to air pollution in their daily lives.

In this randomized, double-blind, placebo-controlled study, we assess the efficacy of 6 weeks of daily supplementation of 200 mg LI3109F (ALV) or a combination of 200 mg LI3109F and 200 mg of licorice root extract (ALV+LR) on indices of respiratory performance, walking capacity, and quality of life measures in healthy adults.

MATERIALS AND METHODS

The study was conducted according to the IHC-GCP guidelines and declaration of Helsinki. The trial was conducted at the clinical study site of the Lakshmi Hospital, Varanasi, Utter Pradesh, India after approval by Opal Institutional Ethics Committee.

The trial was registered with the Clinical Trials Registry of India (CTRI/2020/10/028721), all participants provided written informed consent.

Subjects

105 subjects randomized into three groups (n=35); 18 subjects withdrew from the study leaving 87 completers

Subjects comprised 42 men (40%) and 63 women (60%) at study start

Ages 20- 65 (mean age 47 ± 4.3)

BMI of 22-29.9 kg/m^2 (mean BMI=24.5 ± 1.6 kg/m^2)

Inclusion/Exclusion Criteria

Generally healthy, sedentary, with self-reported sensitivity to air pollution (nasal congestion, sore throat, oro-laryngeal itchiness, cough, hoarse voice)

No chronic respiratory disease, no dietary supplements, no smoking

Experimental Procedures

Randomized, double blind, placebo-controlled, parallel arm clinical study

Study treatments were provided as capsules, taken orally once daily in the morning for six weeks (42 days)

Treatments:

1. 200 mg ALV (*Boswellia serrata, Aegle marmelos [ALV], n=28)*
2. 400 mg ALV +LR *(Boswellia serrata, Aegle marmelos + 200 mg Glycyrrhiza glabra [ALV+LR], n=30)*
3. Matched Placebo Control (PLA, n=29)

Measured Outcomes

Measured at Baseline, Day 21, and Day 42

- Respiratory function: FEV-1 and FVC
- Functional test: Six Minute Walk Test
- Validated questionnaires: Wisconsin Upper Respiratory Symptom Survey (WURSS-21), Immune Status Questionnaire (ISQ), Psychological General Well Being Index (PGWBI)

Measured at Baseline and Day 41

- Biomarkers: CD4+, CD8+, Interleukin-8 (IL-8), Interleukin-4 (IL-4), Interferon-γ (IFN-γ)
- Clinical laboratory and safety tests: hematology, biochemistry, lipids, thyroid, and urinalysis.

Statistical Analysis

Mixed factorial 3x3 or 3x2 ANOVA with repeated measures on the within variable (time), followed by pairwise comparisons between groups at each time and within groups (vs. baseline). Significance was set at p<0.05 adjusted by Bonferroni correction for multiple comparisons.

Table 1. Baseline characteristics.

Parameters	Placebo	ALV	ALV+LR	P-value
N	35	35	35	
Sex (m/f)	10/25	14/21	18/17	
Age (years)	48.4 ± 12.9	44.5 ± 11.8	47.9 ± 12.3	0.593
Height (cm)	160.6 ± 6.2	161.6 ± 6.5	161.5 ± 7.5	0.707
Weight (kg)	62.9 ± 4.8	63.7 ± 4.7	63.8 ± 6.0	0.800
BMI (kg/m^2)	24.6 ± 1.5	24.3 ± 1.3	24.5 ± 1.9	0.543
FEV-1	2.5 ± 0.3	2.8 ± 0.3*	2.8 ± 0.3*	<0.001
FVC	2.8 ± 0.3	2.9 ± 0.4	3.0 ± 0.4*	0.021
SMWT	523.6 ± 15.6	526.0 ± 16.9	521.6 ± 15.0	0.523

Data is presented as means ± standardized deviation of randomized population at study initiation (n=105). P-value derived from univariate ANOVA.

* LI3109F *is commercially available from PLT Health Solutions, Inc.*

RESULTS

Figure 1. Study Design

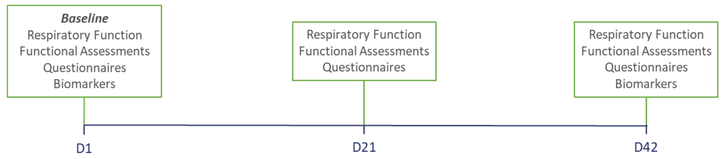
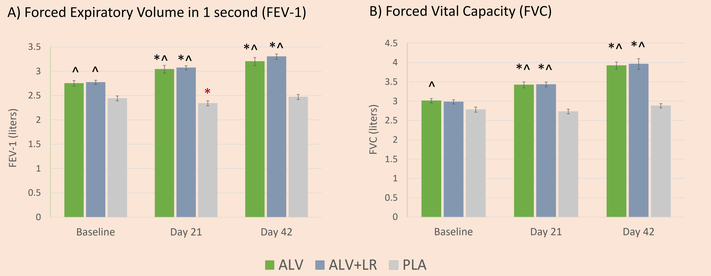
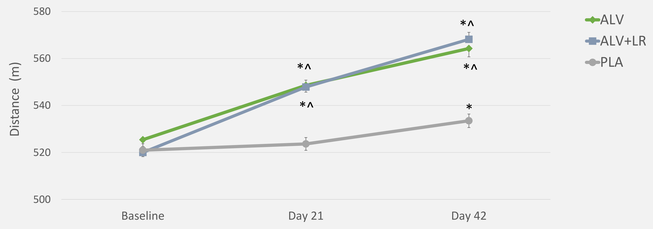


Figure 2. Supplementation improves respiratory function: measures of FEV-1 and FVC at 0, 21, and 42 days.



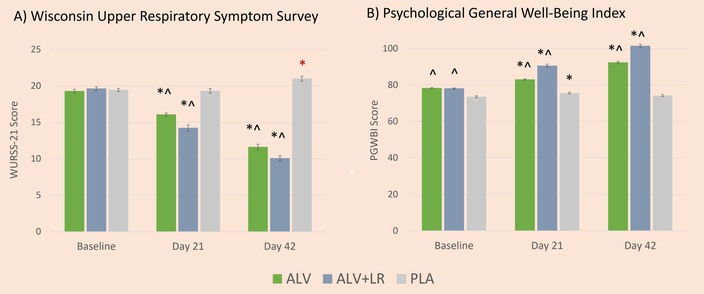
Data are means ± SEM derived from ANOVA adjusted with Bonferroni correction for multiple comparisons. Analysis demonstrated a main effect of time, treatment and a time x treatment interaction effect (p<0.001) for both FEV-1 and FVC. Both treatment groups were significantly improved over PLA (p<0.001), but not different from one another. * Indicates significant within group improvement from baseline, * indicates significant within group decrease from baseline, ^ indicates significant difference between treatment group and placebo at same time point, with significance considered p<0.05.

Figure 3. Supplementation improves functional exercise capacity: measures on the six-minute walk test (SMWT) at 0, 21, and 42 days.



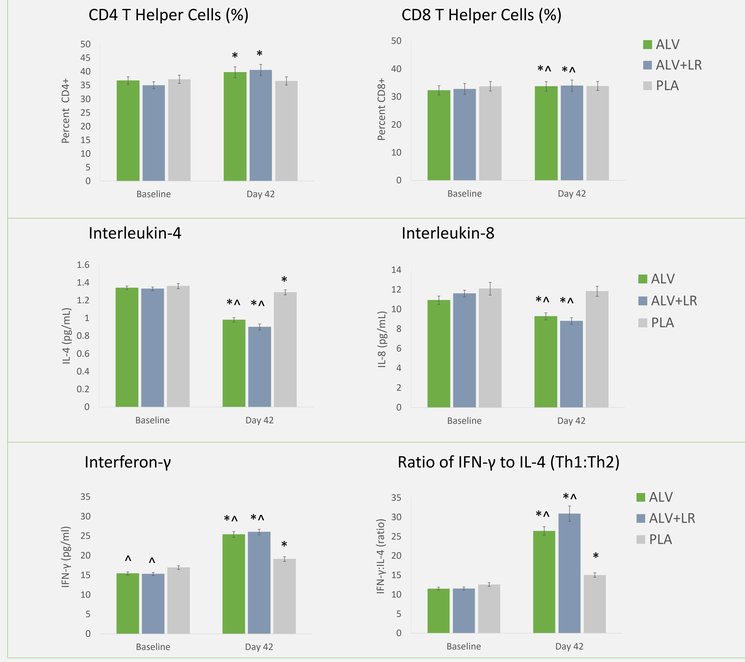
Data are means ± SEM derived from ANOVA adjusted with Bonferroni correction for multiple comparisons. Analysis demonstrated a significant main effect of time, treatment, and a time x treatment interaction effect (p<0.001). Both treatment groups walked significantly farther than PLA (p<0.001) but were not different from one another. * Indicates within-group improvement from baseline, ^ indicates significant difference between treatment group and placebo at same time point, with significance considered p<0.05.

Figure 4. Supplementation decreases symptoms of respiratory irritation and improves sense of well-being: Subjective scores at 0, 21, and 42 days.



Data are means ± SEM derived from ANOVA adjusted with Bonferroni correction for multiple comparisons. Analysis demonstrated a main effect of time, treatment, and a time x treatment interaction (p<0.001) for both WURSS and PGWBI. Both treatment groups reported reduced upper respiratory symptoms and improved general well-being compared to PLA, and ALV+LR scored better than ALV (p<0.001). * Indicates within-group improvement from baseline, * indicates significant within group worsening from baseline, ^ indicates significant difference between treatment group and placebo at same time point, with significance considered p<0.05.

Figure 5. Supplementation decreases markers of inflammation and improves Th1/Th2 balance: measures at 0 and 42 days.



Data are means ± SEM derived from ANOVA adjusted with Bonferroni correction for multiple comparisons. All biomarkers demonstrated a significant (p<0.001) interaction effect, except for CD8+ cells. Treatment groups were different (p<0.05) from PLA on all biomarkers except for CD4+ and CD8+ cells, and treatment groups were not different from one another on any biomarker. * Indicates within-group improvement from baseline, ^ indicates significant difference between treatment group and placebo at same time point, with significance considered p<0.05.

CONCLUSIONS

- Daily supplementation of 200 mg of ALV, with or without an additional 200 mg of licorice root extract (ALV+LR), improved measures of respiratory function in healthy people after 3 and 6 weeks of supplementation. FEV-1 and FVC improved significantly compared to their baseline measures and compared to volumes measured in the placebo group. There was no apparent improvement on these measures when LR was added to ALV.
- Supplementation of ALV or ALV+LR improved functional exercise capacity compared to PLA, as shown by a significant increase in distance walked in the SMWT. Additionally, ALV walked ~39 m and ALV+LR walked ~48 meters farther after 6 weeks of supplementation, meeting the minimally important difference threshold of 30 meters as defined by the American Thoracic Society (7).
- Symptoms of the common cold and upper respiratory irritation decreased in ALV and ALV+LR groups by ~40% and ~49% after six weeks. ALV+LR was significantly improved compared to ALV, but both supplementation regimens improved compared to PLA. While ALV and ALV+LR significantly improved their scores on the WURSS-21, PLA scored worse at the end of the study.
- ALV+LR significantly improved on subjective measures of well-being (PGWBI) compared to ALV, while both supplemented groups improved on this measure compared to PLA. All six domains of PGWBI (anxiety, depression, positive well-being, self control, and general health and vitality) were improved by supplementation.
- CD4+ cells improved over baseline values in supplemented groups only, while there were no measurable differences in CD8+ in any of the three groups. Supplementation decreased levels of pro-inflammatory cytokine IL-8 and Th2-related cytokine IL-4, while increasing the levels of IFN- γ, a Th1 cytokine. Supplementation with either ALV or ALV+LR improved the Th2/Th1 balance away from a profile typically associated with airway inflammation.
- All safety and clinical parameters were within normal levels throughout the study. Overall ALV, with or without LR, appears to safely and effectively improve inflammation, respiratory irritation, and immune dysregulation that can affect healthy people sensitive to air pollution.

CITATIONS

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