

The Effects of Spirulina (*Arthrospira platensis*) Dietary Supplement as an Adjunct Therapy for Children Aged 7-14 Years Old with Asthma: A Randomized, Double-Blind Placebo- Controlled Clinical Trial



Manzon-Reyes, Lou Ver Leigh A., M.D.¹,
Gonzalez-Andaya, Agnes M., M.D.¹

ABSTRACT

Background The anti-inflammatory effect of Spirulina has been demonstrated to inhibit histamine release from mast cell-mediated allergic reactions. Studies have documented the anti-inflammatory and immunomodulatory properties of supplementation as an adjunct therapy for asthma.

Objective To determine the effects of Spirulina supplementation on asthma control and lung function among children aged 7-14 years old.

Methods This is a randomized, double-blind, placebo-controlled study wherein children 7 to 14 years old diagnosed with mild-to-moderate persistent asthma were randomly assigned to receive either Spirulina (1000 mg to 2000 mg daily) or placebo for three months. Asthma Control Test (ACT) and Composite Asthma Severity Index (CASI) were used for patient report-based measures. Forced

expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, and peak expiratory flow rate (PEFR) were determined through spirometry. Post-supplementation assessment for 3 months was done.

Results A total of 39 patients (Spirulina = 20, placebo = 19) were enrolled in this trial. During the supplementation phase, both the Spirulina and placebo groups showed significant improvement in ACT scores (Spirulina, $p < 0.0001$; placebo, $p = 0.19$) compared to baseline. There was no significant change in CASI scores in both groups. However, during the post-supplementation phase, the Spirulina group showed significantly sustained improvement on both the ACT ($p < 0.0001$) and CASI scores ($p < 0.0001$) compared to placebo. The FEV1 ($p = 0.014$), FVC ($p = 0.008$), and PEFR ($p = 0.0001$) of the Spirulina group significantly improved by the end of supplementation. Overall, significant intergroup differences revealed only in FEV1 ($p = 0.0002$) and PEFR ($p < 0.0001$).

Conclusion Daily supplementation with Spirulina significantly improved asthma control, FEV1, and PEFR compared to placebo.

✉ Dr. Lou Ver Leigh A. Manzon-Reyes
louverleigh_md@yahoo.com

¹ Allergy and Immunology Section, Department of Pediatrics, University of Santo Tomas Hospital, Manila, Philippines

Keywords: Spirulina, asthma, spirometry, alternative medicine.

INTRODUCTION

Asthma is the most prevalent chronic disease in children. It is estimated to affect more than 20% of the population in industrialized countries (1). Establishing asthma control is a cornerstone of therapy. The standard treatment for asthma includes inhaled β_2 agonists and inhaled corticosteroids (2). Newer classes of medications have been developed that target mediator release and modify the biologic response. Although current therapies are effective in controlling daily asthma symptoms, continuous and long-term treatment with corticosteroids may pose significant adverse effects, especially in children.

The use of complementary and alternative medicine (CAM) for asthma has been gaining popularity since the 1990s. Multiple herbal medicines and dietary supplements have made positive claims in controlling asthma symptoms. Common CAM medications studied include linden, thyme, stinging nettle, mixed herbal teas, rosehip, and garden sage (3-5).

The dietary supplement Spirulina (*Arthrospira platensis*) is a filamentous blue-green alga that flourishes in various aquatic environments at extremely high pH (6). This cyanobacterium has C-phycoerythrin as its main active ingredient which has been shown to possess numerous potential health benefits (7,8). Due to its high nutritional content and easy digestibility, it has been commercialized as a dietary supplement and used for nutritional build-up of undernourished children. It contains 70% protein, various minerals, vitamins, amino acids, essential fatty acids, carbohydrates, sterols, and blue pigments (phycoerythrins), which help to increase body protein and iron availability and also lower cholesterol and lipid content (9). Spirulina has also demonstrated anti-carcinogenic and anti-inflammatory effects (10-12).

The anti-inflammatory effect of Spirulina has been demonstrated by its capacity to inhibit histamine release from mast cell-mediated allergic reactions. The mechanism of action of Spirulina is likely related to the prevention of calcium release from mast cell stores after the elevation of intracellular cAMP levels brought about by cAMP phosphodiesterase inhibition (13). Previous studies in allergic rhinitis have demonstrated that Spirulina can suppress interleukin 4 (IL-4), thereby inhibiting the T helper 2 (TH2) synthesis

of immunoglobulin E (IgE) (14,15). C-phycoerythrin can selectively inhibit the activity of cyclooxygenase, which is a critical enzyme in the biosynthesis of prostaglandins and displays antioxidative and free radical scavenging properties that may contribute to its anti-inflammatory effects (16). In addition, Spirulina has also been shown to have protective effects on orally-induced food allergy by increasing immunoglobulin A (IgA) antibody and preventing an increase in IgE (17).

The effects of Spirulina in patients with allergic disease have been documented. In a study by Evets et al., 270 children given 5 grams per day of Spirulina tablets for six weeks resulted in the normalization of IgE levels and reduced allergic symptoms (18). In a study by Cingi et al., 2 grams of Spirulina given daily for 6 months significantly improved the symptoms of allergic rhinitis compared with the placebo group ($p < 0.001$) (19). Mao et al. reported that allergic patients consuming 2 grams of Spirulina daily for 12 weeks had reduced production of IL-4 thereby suppressing the differentiation of TH2 cells (20). In a study by Labhe et al., 1 gram of Spirulina administered daily for two months significantly optimized improvement of bronchial asthma when taken together with asthma medications (21).

To date, local data on the effects of Spirulina among the pediatric age group suffering from allergic disorders are limited. The demonstrable potential benefits and safety profile of Spirulina among the older population with allergic disorders may extend to younger allergic patients and may thus provide an additional option of treatment for them.

The aim of this study was to determine the effects of Spirulina supplementation on asthma control among children aged 7-14 years old as to the symptom score using the ACT and the CASI and determine lung function test among asthmatic patients.

METHODOLOGY

The study was a randomized, double-blind, placebo-controlled trial that was conducted at the USTH Outpatient Department. This study was conducted in compliance with the ethical principles of the Declaration of Helsinki and with Good Clinical Practice guidelines. Written informed consent was obtained from all subjects. The protocol was approved by the IRB of the USTH.

Thirty-nine subjects aged 7 to 14 years old with mild-to-moderate persistent asthma were included. The

diagnosis and classification of asthma were based on the Global Initiative for Asthma guidelines and National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR-3), respectively (22).

Subjects presenting with any of the following were excluded from participating in the study: severe persistent or uncontrolled asthma, unremitting chronic illness other than asthma, use of oral or inhaled corticosteroid for more than 6 months, concurrent chemotherapy or immunosuppressive therapy, on immunotherapy, Spirulina or similar herbal supplement intake within 6 months prior to the time of consult, or unlikely compliance with study procedures.

Data on family history of atopy, allergy or asthma, living conditions, environmental and tobacco/cigarette smoke exposure were obtained. Medications taken by the patient and duration of intake were thoroughly investigated. Only short-acting β_2 agonists (SABA), oral steroids, inhaled corticosteroids or combination of inhaled corticosteroids with long-acting β_2 agonist (LABA) and systemic steroids were allowed as medications for mild-to-moderate persistent asthma among patients enrolled in this study.

ACT and CASI were utilized to assess the severity of asthma symptoms in participants.

The ACT score is a reliable and validated tool that measures asthma control. The five-item questionnaire consists of four symptoms (wheezing, coughing, shortness of breath, chest tightness), need for rescue inhaler or nebulizer medication, and a patient self-assessed level of control in the past four weeks. The total score ranges from 5 to 25. A score below the cut-off point of 19 indicates poor asthma control (23).

The CASI is another validated tool that measures asthma control and provides quantification of asthma severity. The CASI score incorporates the five domains of day symptoms and salbutamol use, night symptoms and salbutamol use, controller treatment, lung function measures, and exacerbations. The maximum possible score is 20 indicating poor asthma control and disease severity (24).

Clinical evaluations using different scoring systems were performed solely by the primary investigator throughout the study period.

All study participants may withdraw from the study at any time at their own request or at the responsible discretion of the investigator. Patients who were not able to commit to follow-up visits or signified an inability to comply with taking the daily

Spirulina supplement or placebo were automatically not included, but follow-up care was still provided for them. Those who had completed treatment for 1 to 2 months and consequently withdrew their participation from the study were included in the intention-to-treat group. Subjects who withdrew from the study were immediately replaced by new participants only up to the fifth month of the study period, i.e., patients who withdrew from the study after this date were not anymore replaced.

Spirometry using the KoKo Spirometer with a Fleisch-type pneumotach was performed on all patients. The following parameters were measured: FEV1, FVC, the ratio of FEV1 to FVC (FEV1/FVC), and PEFr.

Each subject enrolled into the study was assigned a subject identification number. Patients were randomized on a 1:1 basis (computer-generated randomization list) to receive the proprietary Spirulina-based dietary supplement, CELLIFE (Pharmaceia Jimenez) or placebo (25). Based on the manufacturer's recommended dose, children aged 7 to 10 years old received two tablets of Spirulina 250 mg twice a day, which was equivalent to 1000 mg per day, while those aged 11 to 14 years old received four tablets twice a day, which was equivalent to 2000 mg per day. The placebo group took tablets that were color-matched and of the same weight as Cellife but was made of inert material and without nutritional content. Medicines were placed in color-matched bottles labelled with coded numbers unknown to the patient or the investigator. Pharmaceia Jimenez Corp. CELLIFE was duly authorized to keep the codes confidential, but codes were broken in cases of emergency or a serious adverse event.

Each patient was instructed to take the study medication daily for 3 months without discontinuing any of their regular medications for asthma. Study medications were dispensed upon inclusion in the study (baseline or week 0) and during subsequent visits scheduled at weeks 2, 4, 8, and 12 after enrollment. Any unused study drug previously dispensed was asked to be returned on their next visit. Any participant found to be taking 20% more or less than the prescribed study medication were counseled on the importance of following their recommended dosing schedule. With each follow-up visit, review of symptoms, ACT and CASI scoring, physical examination, and spirometry were carried out. Furthermore, post-supplementation follow-up of symptoms and physical examination were done for each subject at 4,

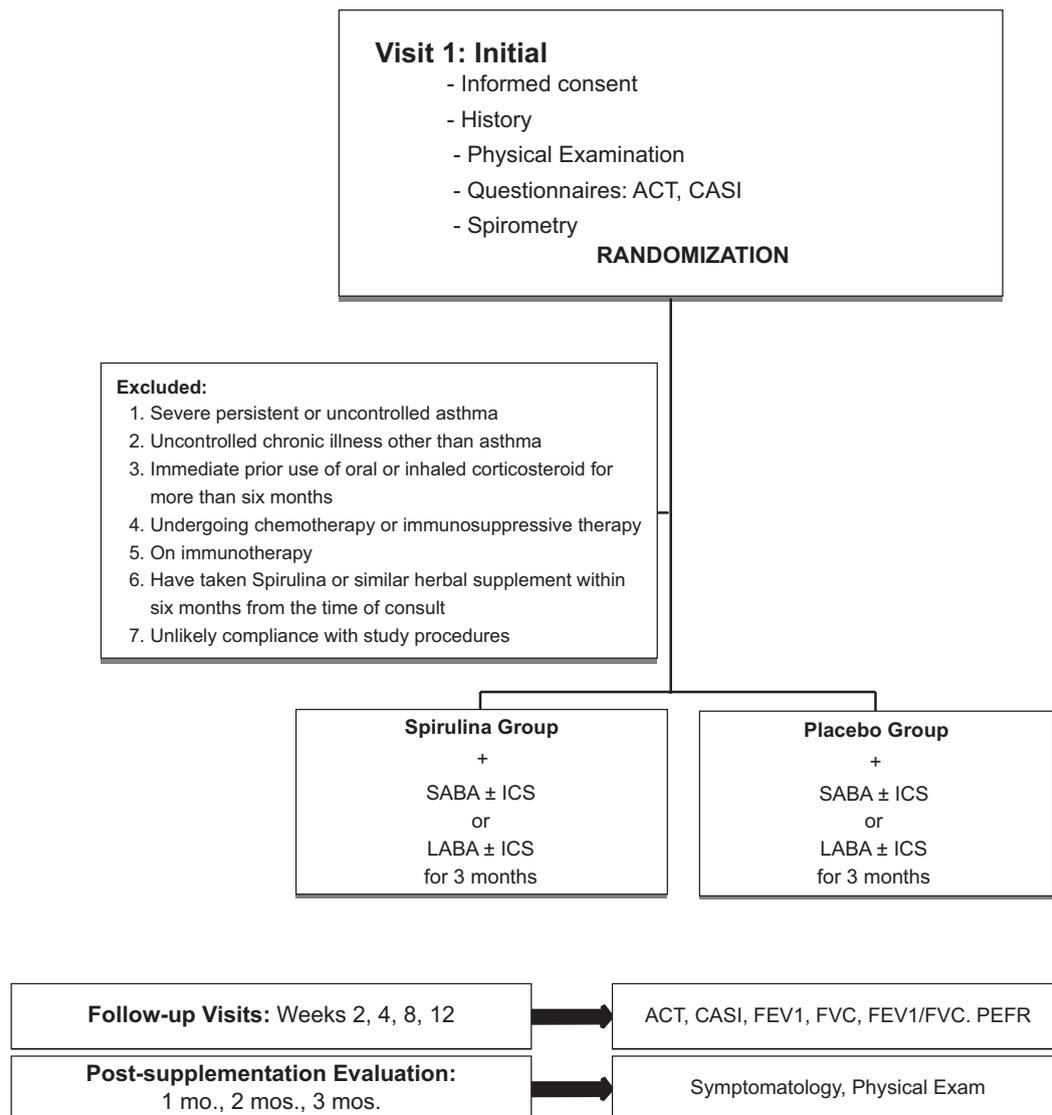


Figure 1. Consort Diagram of the Spirulina Clinical Trial. SABA, short-acting β 2 agonist. LABA, long-acting β 2 agonist. ICS, inhaled corticosteroids. ACT, Asthma Control TestTM. CASI, Composite Asthma Severity Index.

5, and 6 months from the beginning of treatment. Figure 1 summarizes the methodology.

Data was encoded and analyzed using SPSS v10. Descriptive statistics were generated for all variables. For nominal data, frequencies and percentages were computed. For numerical data, mean and standard deviations (SD) were generated. Paired T-test was applied to asthma symptom scores and Wilcoxon signed rank test to measures of pulmonary function to compare before and after treatment values. In detecting the overall differences over time, repeated measures ANOVA was used on pulmonary function tests and Friedman test (nonparametric counterpart) on asthma scores.

During data collection, the participants were monitored for any adverse events, regardless of the treatment group they belonged to. Possible adverse effects

associated with intake of Spirulina include diarrhea, constipation, and allergic reactions (e.g. rashes). The occurrence of any adverse event was reported immediately to the primary investigator and IRB. Sufficient information was obtained by the investigator to assess causality and these were followed up until the event or its sequelae had resolved or stabilized to an acceptable level. Emergency medical treatment was provided free for subjects when needed.

RESULTS

Thirty-nine patients with bronchial asthma ranging between 7 to 14 years were enrolled in the clinical trial from October 2013 to June 2014. The subjects were randomly divided into two groups wherein 20 subjects received the proprietary Spirulina-based

TABLE 1. Demographics and Characteristics of the 39 Subjects in the Spirulina Trial.

	Spirulina (n=20)	Placebo (n=19)	p value
	n (%) or Mean \pm SD		
Female	6 (30)	9 (47)	0.267
Age (years)	9.95 \pm 1.99	9.53 \pm 1.90	0.500
Body weight (kilograms)	32.33 \pm 9.52	30.29 \pm 7.32	0.459
Height (centimeters)	139.07 \pm 14.75	134.65 \pm 12.78	0.322
Body Mass Index	16.54 \pm 3.51	17.05 \pm 3.28	0.641
Past illnesses			
Atopic dermatitis	1 (5)	2 (10)	0.516
Allergic rhinitis	10 (50)	13 (68)	0.242
Bronchial asthma	20 (100)	19 (100)	
Admission in past 12 months			
Emergency room	5 (25)	4 (21)	0.772
Hospital	4 (20)	1 (5)	0.168
Environmental exposures			
Industrial or automotive smoke	6 (30)	7 (37)	0.653
Cigarette or tobacco smoke	11 (55)	10 (53)	0.881
Animal fur or dander	5 (25)	6 (32)	0.645

dietary supplement and 19 subjects received the placebo supplement. The sociodemographic characteristics of gender, age, weight, height, body mass index, and medical history were not significantly different between the two groups (Table 1).

Effect of Spirulina and placebo on ACT and CASI scores

After 3 months of supplementation, improvement in the median ACT scores was observed in both the Spirulina (score of 14.5 to 22, $p < 0.0001$) and placebo groups (score of 18 to 20, $p = 0.019$). However, CASI scores decreased after 3 months of supplementation for both groups, but these changes were not statistically significant (Table 2).

Post-supplementation, the Spirulina group remained to have significantly higher ACT scores than the placebo group (from a score of 15 to 25 versus 18 to 20, $p < 0.0001$; Figure 2).

At 2 months from baseline, median CASI scores fell from 7 to 3 in both groups. CASI scores in the Spirulina group significantly decreased further to 2- at 1-month post-supplementation before it finally levelled off ($p < 0.0001$; Figure 3).

Effect of Spirulina and placebo on pulmonary function tests

After 3 months of supplementation, pulmonary function test results improved from baseline in both groups.

However, significant changes were only found in the FEV1 ($p = 0.014$), FVC ($p = 0.008$), and PEFR ($p = 0.0001$) of the Spirulina group compared to placebo (Table 3). At the beginning of supplementation, the FEV1 performance of the Spirulina group was slightly lower than that of placebo, but a trend reversal was reached by the second month. From then on, the Spirulina group showed significant improvement in FEV1 over the next 4 months ($p = 0.0002$; Figure 4).

There was no significant change in the FVCs of both groups during the 6-month observation period ($p = 0.4182$; Figure 5). In both groups, FVCs increased by the second month of supplementation and changed relatively little thereafter.

The FEV1 to FVC ratios of the two groups did not differ significantly from one another throughout the observation period ($p = 0.1403$; Figure 6).

The PEFR averages significantly increased steadily over time in the Spirulina group compared to the placebo where values remained close to baseline levels ($p < 0.0001$; Figure 7).

Safety and tolerability were assessed by adverse events reported by subjects at each post-randomization clinic visit. There were no adverse events reported such as diarrhea, constipation, or allergic reactions directly attributed to the supplements given between the groups during the study period.

TABLE 2. Asthma Symptom Scores at Baseline and 3 Months (End of Treatment) in the Spirulina and Placebo Groups^a

	Spirulina			Placebo		
	Baseline	3 months	<i>p</i> -value	Baseline	3 months	<i>p</i> -value
ACT [*]	14.5	22.0	<0.0001	18.0	20.0	0.019
CASI [†]	6.5	3.0	1.000	7.0	3.0	0.999

^aScores are given as medians. Significant *p* values <0.05 are in boldface.

^{*}Higher value indicates better asthma control.

[†]Lower value is indicative of better asthma control.

ACT, Asthma Control Test. CASI, Composite Asthma Severity Index.

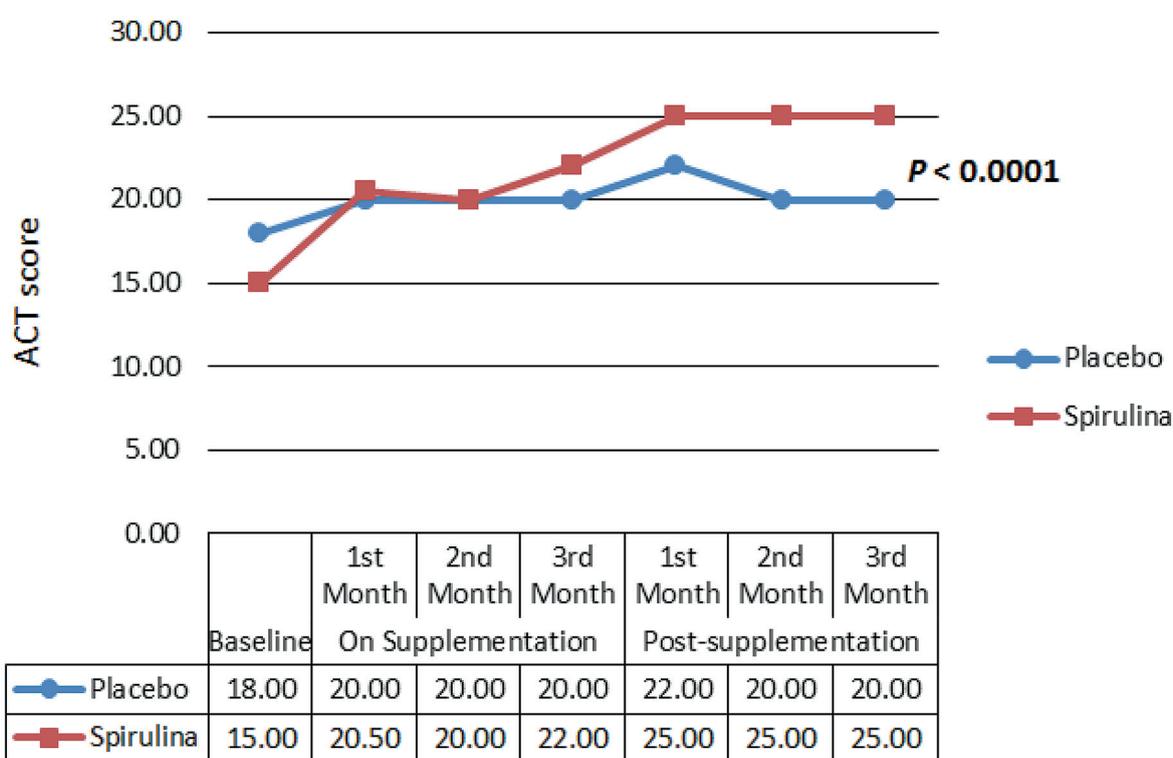


Figure 2. Median ACT scores of the Spirulina and placebo groups over six months.

DISCUSSION

This double-blind, randomized, placebo-controlled study has demonstrated that Spirulina supplementation for three months was effective in improving asthma symptoms and lung function in asthmatic children. During the supplementation phase, Spirulina was as effective as placebo in improving asthma symptom scores. However, post-supplementation asthma symptom scores significantly improved over time in the Spirulina group compared to placebo. Daily intake of Spirulina significantly improved pulmonary function tests as demonstrated by increased FEV1 and PEFR in the Spirulina group compared to placebo. The tolerability profile of Spirulina was comparable to placebo and no serious adverse effects were encountered.

The anti-inflammatory effects of Spirulina are related to its ability to inhibit calcium release from mast

cell stores after the elevation of intracellular cAMP within 10 seconds (13). In acute asthma exacerbation, Spirulina can inhibit release of pro-inflammatory mediators such as histamine, tumor necrosis factor-alpha (TNF- α), and vascular permeability factor or vascular endothelial cell growth factor from mast cells (26,27). Newly synthesized lipid mediators such as prostaglandin D2, leukotrienes (LTC4, LTD4, LTE4, LTB4) and platelet-activating factor (PAF), as well as reactive oxygen species (ROS) are also released from mast cells during IgE-dependent allergic reactions. Previous animal studies have shown that in arachidonic acid-induced inflammation, Spirulina can significantly reduce LTB4 and prostaglandin E2 levels (28,29).

In this study, both the Spirulina and placebo groups showed improvement in asthma symptom score during the supplementation phase. During this time, both study groups were still receiving standard maintenance

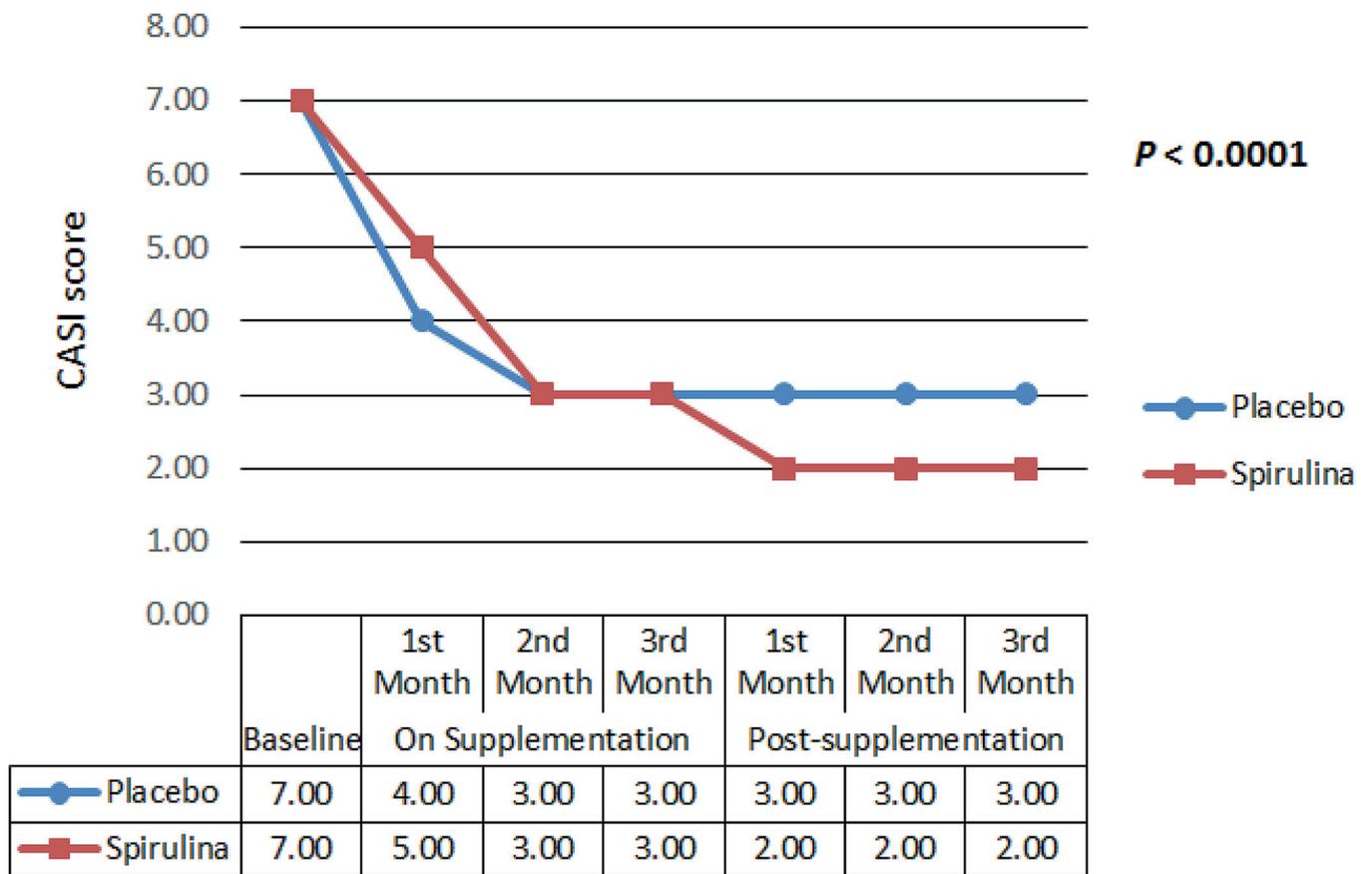


Figure 3. Median ACT scores of the Spirulina and placebo groups over six months.

TABLE 3. Pulmonary Function Tests at Baseline and 3 Months (End of Treatment) in the Spirulina and Placebo Groups^a

	Spirulina			Placebo		
	Baseline	3 months	p-value	Baseline	3 months	p-value
FEV1	56.55 ± 31.06	72.75 ± 24.15	0.014	65.79 ± 28.58	68.89 ± 25.02	0.296
FVC	62.95 ± 30.33	79.5 ± 16.88	0.008	66.95 ± 26.26	75.32 ± 21.48	0.071
FEV1/FVC	80.80 ± 32.69	92.05 ± 22.38	0.088	94.42 ± 27.04	91.05 ± 15.46	0.692
PEFR	36.85 ± 23.88	56 ± 23.51	0.0001	46.05 ± 25.62	50.16 ± 24.37	0.252

^a Before and after values are given as mean ± SD. Significant p values <0.05 are in boldface. FEV1, forced expiratory volume at 1 second. FVC, forced vital capacity. PEFR, peak expiratory flow rate.

medications for asthma, i.e., short-acting or long-acting beta agonist plus inhaled corticosteroids. This may have contributed in part to the control of asthma symptoms in both groups during the supplementation phase.

Taking together the results presented, extended supplementation with Spirulina appeared to have targeted both preformed and newly synthesized mediator release from mast cells as reflected by more significant and sustained improvement in both patient-reported symptoms and objective measures of asthma control compared to placebo.

The long-term immunomodulatory effect of Spirulina was demonstrated in previous studies. Mao et al. have shown that after 12 weeks of supplementation with Spirulina, there was a significant decrease in IL-4 by 32% (20). IL-4 is a critical cytokine involved in type I hypersensitivity reactions and it effectively promotes IgE production. Decreased production of IL-4, therefore, aids in shifting the humoral-mediated immunity towards TH1 differentiation leading to less allergic responses.

In addition, Spirulina has also been shown to potentiate the function of the immune system. Hirashi et

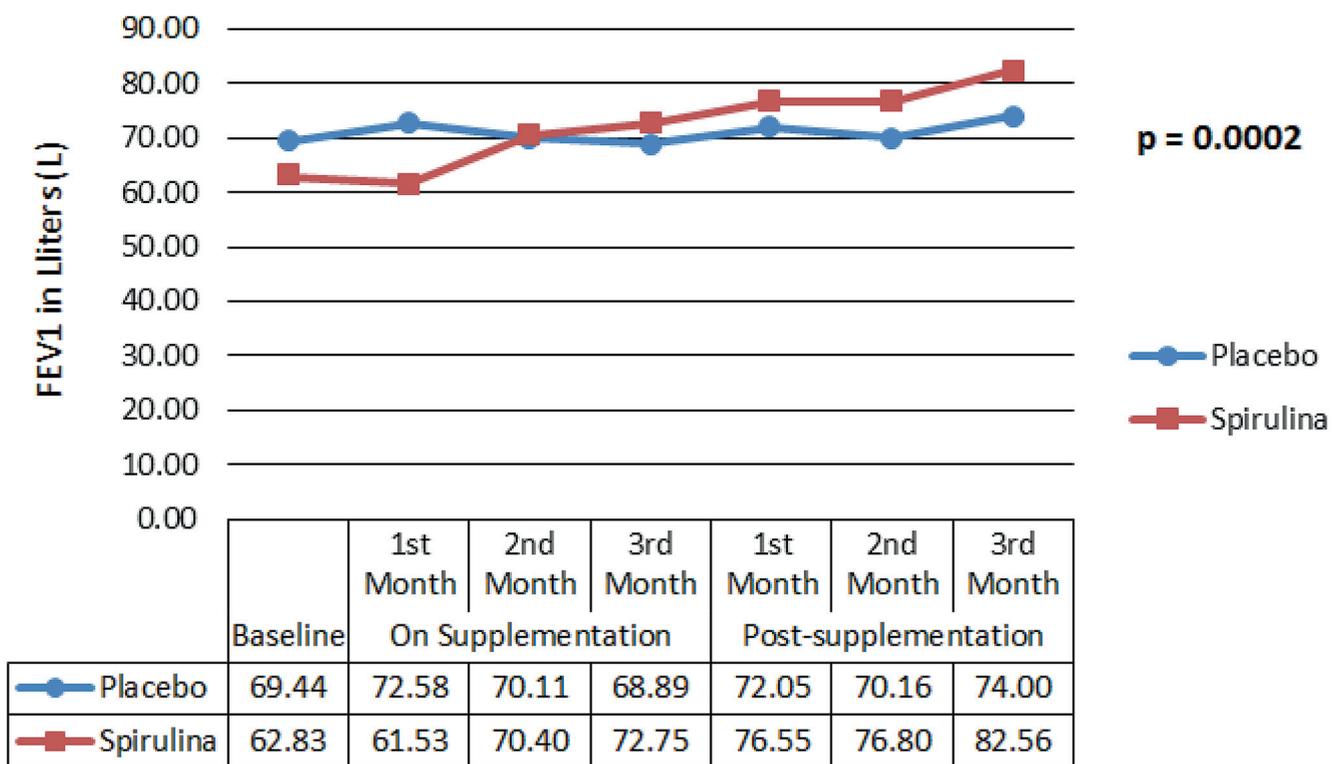


Figure 4. Effect of Spirulina on FEV1 of the Spirulina and placebo groups over six months.

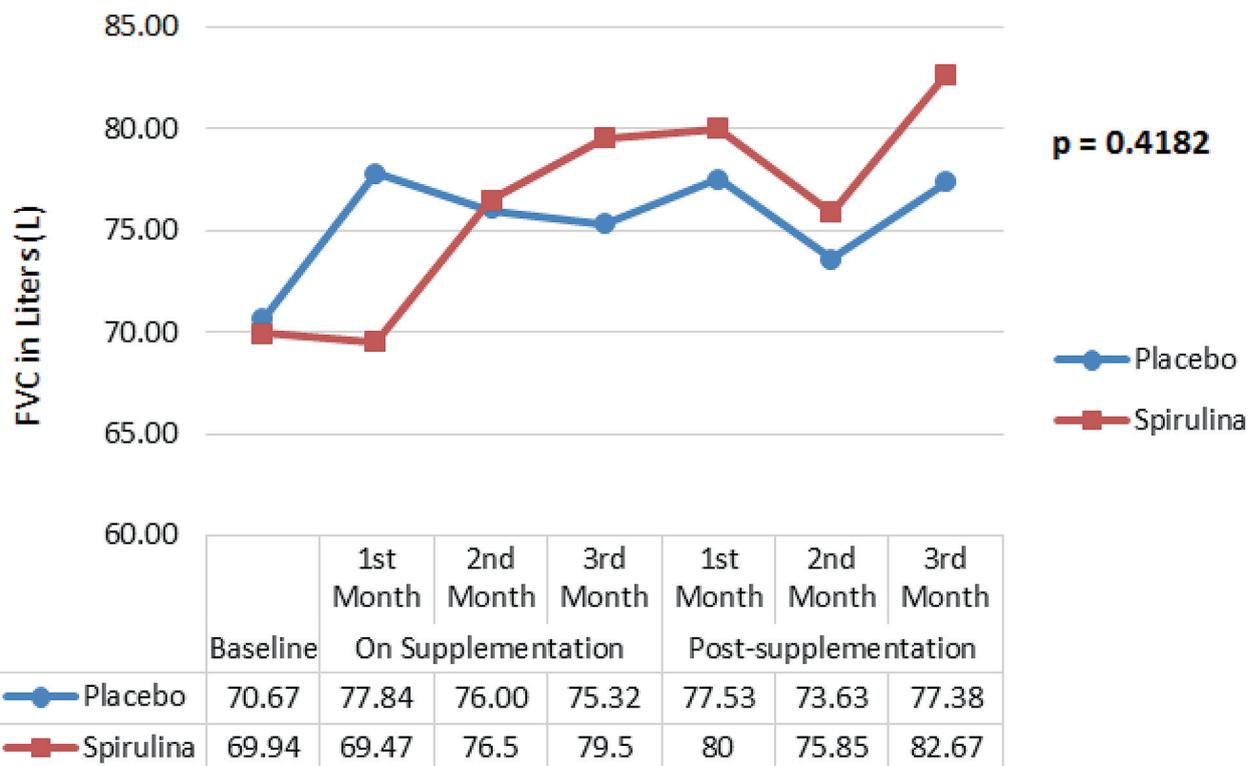


Figure 5. Effect of Spirulina on FVC of the Spirulina and placebo groups over six months.

al. reported that both interferon gamma (IFN- γ) and cytotoxicity are upregulated in more than 50% of the patients taking 1,000 to 8,000 mg of Spirulina extract

orally for a total of eight weeks (12). The direct immunomodulatory effects of Spirulina on myeloid lineages and natural killer (NK) cells has been ascribed

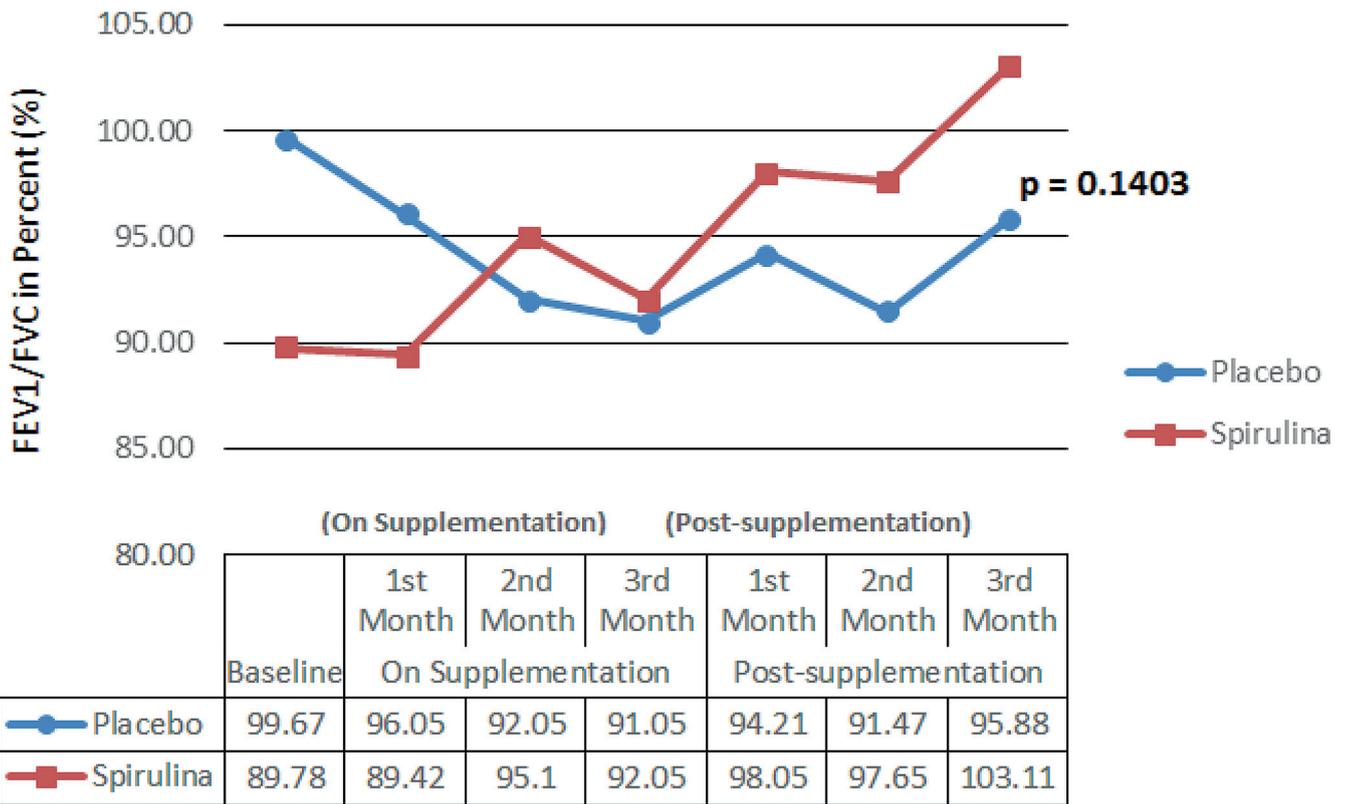


Figure 6. Effect of Spirulina on FEV1/FVC of the Spirulina and placebo groups over six months.

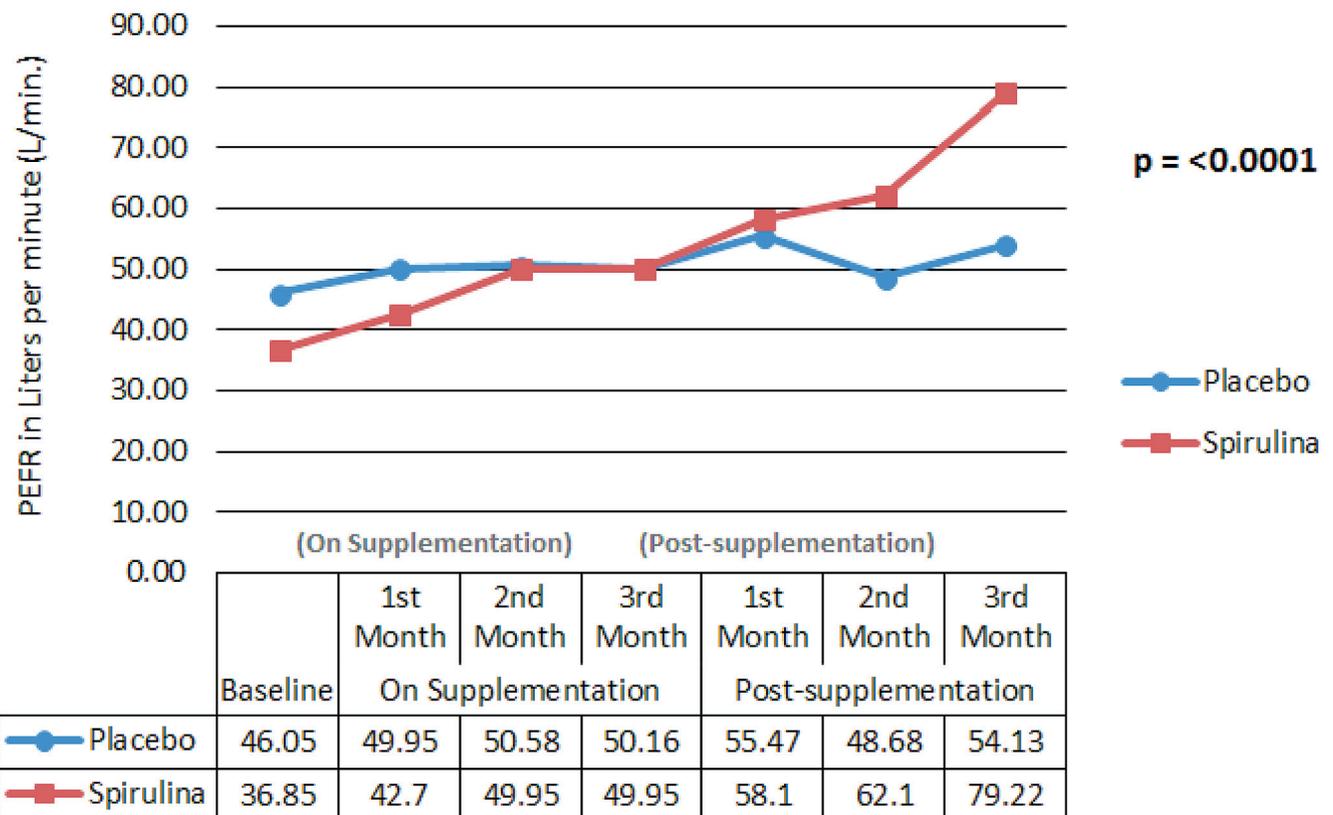


Figure 7. Effect of Spirulina on PEFR of the Spirulina and placebo groups over six months.

through its signalling responses in Toll-like receptors. This implies that Spirulina may also provide additional benefit as an antibacterial or antiviral agent (30).

Overall, Spirulina has been classified as a Generally Recognized as Safe (GRAS) substance by the United States Food and Drug Administration (FDA) (31-33). Human clinical trials and animal studies have supported the safety and nutritional benefits of Spirulina. The pigment C-phycoerythrin in Spirulina has been classified into the "practically nontoxic" category. Moreover, daily consumption of 4,132 mg/kg body weight of Spirulina among humans did not result in any adverse effects even in infants and young children (34,35).

The present study is the first local study to measure asthma symptom scores using combined ACT and CASI with lung function assessment using spirometry. Both the ACT and CASI scores are reliable and validated tools to measure asthma control. Wildfire et al. reported that using CASI detected 32% larger improvement in asthma control than by reported symptoms alone (24). One strength of this study is the use of CASI, in addition to the ACT score, which provided a more comprehensive assessment of asthma control and severity of symptoms in response to the investigational drug, Spirulina.

In the present study, it was shown that Spirulina was as effective as placebo in improving asthma symptom scores after three months of supplementation. However, improved asthma symptom scores were significantly sustained in the Spirulina group even after discontinuing the supplement compared to placebo. These results

indicate that patient-reported improvement in asthma symptoms were achieved as early as three months after supplementation with Spirulina and this effect was sustained for a longer time compared to placebo.

In the diagnosis of asthma, reversibility in PEFr and rise in FEV1 after an inhaled β_2 -agonist are the most frequently used indices for assessing airway obstruction (23,24). The present study has demonstrated that FEV1 and PEFr significantly improved in the Spirulina group compared to placebo. In this study, improvement in lung function tests was achieved as early as two months and three months in FEV1 and PEFr, respectively. Similar results were observed in the study by Labhe et al. which showed that extended supplementation with Spirulina plus medication over a period of two months resulted in increased lung function efficacy. This indicates a long-term sustainable effect of Spirulina in relieving bronchial obstruction (21).

CONCLUSION

This study has shown that in children with mild-to-moderate persistent asthma, supplementation with Spirulina at a dose of 1,000 to 2,000 mg per day for three months was safe and associated with improvement in asthma symptoms as measured by increased ACT scores, reduced CASI scores, and improvement of FEV1 and PEFr. Moreover, even after cessation of supplementation with Spirulina, the reported subjective benefits and objective outcome measures were significantly sustained until the end of the 6-month observation period.

ACKNOWLEDGMENTS

This work was supported in part by CELLIFE Spirulina (Pharmaceia Jimenez).

It was agreed upon with the manufacturer and distributor of Cellife Spirulina (Pharmaceia Jimenez) that any information collected or generated by the investigator will be published, whether the results were favorable to the investigational drug or not. CELLIFE was provided the opportunity to review any proposed publication or another type of disclosure at least 30 days before the final manuscript was submitted to a publishing company.

Conflict(s) of Interest There are no conflicts of interest in the authorship or publication of this manuscript.

Financial Support No financial support was provided in this manuscript. Material support for this research and work are clearly identified in the acknowledgments section of this manuscript.

REFERENCES

- Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema: ISAAC. The International Study of Asthma and Allergies In Childhood (ISAAC) Steering Committee. *Lancet*. 1998;351:1225-1232.
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2012 [Internet]. [updated 2012; cited 2014 Jul 29]. Available from: <http://www.ginasthma.org/>.
- Bielory L. Complementary and alternative interventions in asthma, allergy, and immunology. *Ann Allergy Asthma Immunol*. 2004;93:S45-S54.
- Philp J, Maselli J, Pachter I, et al. Complementary and alternative medicine use and adherence with pediatric asthma treatment. *Pediatrics*. 2012;129:1-7.
- Kurt E, Bavbek S, Pasaoglu G, et al. Use of alternative medicines by allergic patients in Turkey. *Allergol et Immunopathol*. 2004;32(5):289-94.
- Nuhu A. Spirulina (Arthrospira): an important source of nutritional and medicinal compounds. *Journal of Marine Biology*. 2013;2013:1-8.
- Kumari D, Jaffar B, Prasad M, et al. Potential benefits of Spirulina platensis. *Pharmanest*. 2011;2:417-422.
- Kamenidou I, Aggelopoulos S, Batzios A. Natural medicinal attributes and benefits of Spirulina: segmentation based on consumers' knowledge. *J Med Plant Res*. 2011;5(14):3192-99.
- Jassby A. Spirulina: a model for micro algae as human food. In: Lembi CA, Waaland JR, editors. *Algae and human affairs*. Cambridge: Cambridge University Press; 1988.
- Chamorro-Cevallo G, Garduño-Siciliano L, Barrón B, et al. Chemoprotective effect of Spirulina (Arthrospira) against cyclophosphamide-induced mutagenicity in mice. *Food Chem Toxicol*. 2008;46(2):567-74.
- Orhan F, Sekerel B, Kocabas C, et al. Complementary and alternative medicine in children with asthma. *Ann Allergy Asthma Immunol*. 2003;90:611-615.
- Hirashi T, Matsumoto M, Hazeki K, et al. Activation of human innate immune system by Spirulina: augmentation of interferon production and NK cytotoxicity by oral administration of hot water extract of Spirulina platensis. *Int Immunopharmacol*. 2002;2(4):423-34.
- Shih C, Cheng S, Wong C, et al. Anti-inflammatory and anti-hyperalgesic activity of C-phycoerythrin. *Anesth Analg*. 2009;108:1303-10.
- Chen LL, Zhang SF, Huang DN, et al. Experimental study of Spirulina platensis in treating allergic rhinitis in rats. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2005;30(1):96-98.
- Reddy CM, Bhat VB, Kiranmai G, et al. Selective inhibition of cyclooxygenase-2 by C-phycoerythrin, a biliprotein from Spirulina platensis. *Biochem Biophys Res Commun*. 2000;277:599-603.
- Romay C, Armesto J, Remirez D, et al. Antioxidant and anti-inflammatory properties of C-phycoerythrin from blue-green algae. *Inflamm Res*. 1998;47:36-41.
- Hayashi O, Hirahashi T, Katoh T, et al. Class specific influence of dietary Spirulina platensis on antibody production in mice. *J Nutr Sci Vitaminol (Tokyo)*. 1998;44:841-851.
- Evets L. Means to normalize the levels of immunoglobulin E, using the food supplement Spirulina [Internet]. 1994. Grodenski State Medical Univ. Russian Federation Committee of Patents and Trade. Patent (19) RU (11)2005486.1994. Available from: http://www.iimsam.org/publications_and_reports.php.
- Cingi C, Conk-Dalay M, Cakli H, et al. The effects of spirulina on allergic rhinitis. *Eur Arch Otorhinolaryngol*. 2008;265:1219-23.
- Mao T, Van de Water J, Gershwin M. Effects of a Spirulina-based dietary supplement on cytokine production from allergic rhinitis patients. *J Med Food*. 2005;8(1):27-30.
- Labhe R, Mani U, Iyer U, et al. The effect of spirulina in the treatment of bronchial asthma. *J Nutraceut Function Med Foods*. 2001;3(4):53-60.
- Busse W. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol*. 2007;138.
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2014 [Internet]. [updated 2014; cited 2014 Aug 20]. Available from: <http://www.ginasthma.org/>.
- Wildfire JJ, Gergen PJ, Sorkness CA, Mitchell HE, Calatroni A, Kattan M, et al. Development and validation of the Composite Asthma Severity Index—an outcome measure for use in children and adolescents. *J Allergy Clin Immunol*. 2012;129(3):694-701. doi: 10.1016/j.jaci.2011.12.962.
- Dallal G. Randomization.com [Internet]. 2007 [updated 2013 Mar 29; cited 2014 Jul 29]. Available from: <http://www.randomization.com>.
- Remirez D, Ledon N, Gonzalez R. Role of histamine in the inhibitory effects of phycoerythrin in experimental models of allergic inflammatory response. *Mediators of Inflammation*. 2002;11:81-85.
- Yang H, Lee E, Kim H. Spirulina platensis inhibits anaphylactic reaction. *Life Sciences*. 1997;61:1237-44.
- Romay C, Ledon N, Gonzalez R. Effects of phycoerythrin extract on prostaglandin E2 levels in mouse ear inflammation test. *Arzneim Forsch/Drug Res*. 2000;50:1106-1109.
- Romay C, Ledon N, Gonzalez R. Phycoerythrin extract reduces leukotrienes B4 levels in arachidonic acid-induced mouse ear inflammation test. *J Phar Pharmacol*. 1999;51:641-642.

30. Mainardi T, Kapoor S, Bielory L. Complementary and alternative medicine: Herbs, phytochemicals and vitamins and their immunologic effects. *J Allergy Clin Immunol.* 2009;123:283-94.
31. FDA. GRN 000127. Spirulina, the dried biomass of *Arthrospira platensis* [Internet]. 2003. Available from: <http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=grasListing&id=127>.
32. Chamorro GA, Herrera G, Salazar M, et al. Subchronic toxicity study in rats fed Spirulina. *J Pharm Belg.* 1988;43(1):29-36.
33. Chamorro G, Salazar M, Favila L, et al. Pharmacology and toxicology of Spirulina alga. *Rev Invest Clin.* 1996;48:389-99.
34. Simpore J, Kabore F, Zongo F, Dansou D, Bere A, Pignatelli S, et al. Nutrition rehabilitation of undernourished children utilizing Spirulina and Misola. *Nutr J.* 2006;5:3-7.
35. Simpore J, Zongo F, Kabore F, Dansou D, Bere A, Nikiema JB, et al. Nutrition rehabilitation of HIV-infected and HIV-negative undernourished children utilizing spirulina. *Ann Nutr Metab.* 2005;49:373-80.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.