Consumption of an aqueous cyanophyta extract derived from *Arthrospira platensis* is associated with reduction of chronic pain: results from two human clinical pilot studies

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### Objectives:
The aim of this study was to evaluate the effects of consumption of an aqueous cyanophyta extract (ACE) from *Arthrospira platensis* on chronic pain in humans, in two clinical pilot studies.

### Design and interventions:
The two pilot studies each involved 12 subjects experiencing chronic pain. The initial study followed an open-label 4-week study design involving consumption of 1 g ACE per day. A subsequent placebo-controlled, single-blind, crossover study involved consumption of 500 mg ACE, 250 mg ACE, or 0 mg ACE (placebo) per day for 1-week duration, separated by 1-week washout period.

### Subjects:
Adult subjects of both sexes, with chronic joint-related pain for at least 6 months prior to enrollment, were recruited after obtaining written informed consent.

### Outcome measures:
Visual analog scales were used to score pain at rest and during physical activity for each person’s primary and secondary areas of chronic pain. An activities of daily living questionnaire was used to collect data on physical functioning.

### Results:
The data showed rapid reduction of chronic pain in people consuming ACE, where the reduction in pain scores for each person’s primary pain area reached a high level of statistical significance after 2 weeks of consumption (*P*<0.01), both when at rest and when being physically active. Secondary pain areas when physically active showed highly significant improvements within 1 week of consumption of 1 g/d (*P*<0.001) and borderline significant improvements within 1 week of consuming 500 mg/d (*P*<0.065) and 250 mg/d (*P*<0.05). This was accompanied by an increased ability to perform daily activities (*P*<0.05). A small but significant weight loss was observed during the 4-week study, as the average body mass index dropped from 31.4 to 29.4 (*P*<0.01).

### Conclusion:
Consumption of ACE was associated with reduction of chronic pain, as well as a dose-dependent increased ability to perform activities of daily living.

### Keywords:
activities of daily living, pilot study, placebo-controlled study, Spirulina

### Introduction
Chronic joint-associated pain increases with age as a result of mechanical stress and aging and is confounded by states of chronic inflammation. The escalating need for natural methods for pain management has led to an increased interest in natural methods for reducing pain, pain perception, and inflammation. Acute pain is an essential function of our body’s defense system as it stimulates motor responses to potentially dangerous stimuli. Despite pain being a sensory quality, and therefore subjective,
it has a molecular basis including synaptic transmission and the release of excitatory neurotransmitters. Chronic pain, on the other hand, has no protective purpose and has been linked to the development of lowered pain thresholds due to the prolonged activation of low-threshold mechanoreceptive fibers. These changes in pain thresholds can result in altered pain perception and body posture compensation, which further accelerates the degradation of joint structures and reduces their functionality.

The inflammatory cascade is a response specific to our innate immune system and involves the release of inflammatory mediators from affected cells, the production of prostaglandins via cyclooxygenase (COX-1 and COX-2) activity, and the release of cytokines and growth factors from recruited immune cells. Cytokines play a role in the initiation and maintenance of inflammatory states by either acting on nociceptors or indirectly stimulating the release of prostaglandins. This enhances nociceptor sensitization by reducing the activation threshold for inflammatory mediators. If inflammatory conditions persist, the activation of kinase cascades results in transcriptional changes that can lead to lowered response thresholds and heightened reactions to stimuli. In addition, sites of chronic inflammation have been linked to the origination of a variety of degenerative diseases, due to the degradation of cartilage, and linked to cancers due to DNA damage associated with persisting inflammatory and immune factors.

In addition to their roles in the maintenance of inflammatory states, several proinflammatory cytokines have been observed to be involved in the initiation and persistence of pathological pain through their actions on nociceptive sensory neurons. For example, neurotrophic growth factors significantly affect neuronal sensitivity during inflammation, and increased levels of neurotrophic growth factors have been implicated in inflammatory disorders such as arthritis. As pain perception involves both increased production of prostaglandins by inflammatory enzymes and signal transduction pathways in the nervous system, efforts to reduce pain commonly involve both pain-reducing and anti-inflammatory measures. Currently, there is a growing interest in identifying natural products for the reduction of inflammatory states, several proinflammatory cytokines have been implicated in inflammatory disorders such as arthritis. As pain perception involves both increased production of prostaglandins by inflammatory enzymes and signal transduction pathways in the nervous system, efforts to reduce pain commonly involve both pain-reducing and anti-inflammatory measures. Currently, there is a growing interest in identifying natural products for the reduction of inflammatory and the associated pain as alternatives to steroidal and nonsteroidal anti-inflammatory medications. By targeting and inhibiting inflammatory pathways in a comparable way to nonsteroidal anti-inflammatory medications, natural compounds may reduce inflammatory immune responses without the side effects of prescription medications.

Antinociceptive and anti-inflammatory properties have been attributed to species of *Arthospira* cyanobacteria (such as *Arthospira maxima* and *Arthospira platensis*), due to their naturally high concentrations of phycocyanin, phenolic compounds, and carotenoids. Lipid extracts of several species of blue-green algae were shown to decrease the nuclear translocation of nuclear factor-κB, thus contributing to decreased expression and secretion of proinflammatory cytokines. The pharmacological properties of phycocyanin, one of the photosynthetic components of blue-green algae, have been linked to its ability to inhibit COX-2 enzymatic activity and to inhibit lipid peroxidation and to scavenge free radicals in vitro. Phenolic compounds and carotenoids exhibit strong antioxidant properties, as they are efficient scavengers of peroxyl radicals and can donate their phenolic hydrogen atoms to neutralize free radical molecules. In addition, previous studies have demonstrated the clinical significance of the biological activities of *Arthospira*. Specifically, *Arthospira* supplementation has been linked to hypocholesterolemic effects, hepatoprotective properties via hypolipidemic effects, blood pressure reductions in hypertensive patients, improved anemia and immunosenescence in senior citizens, and beneficial effects on blood lipid profiles in patients with metabolic dysfunction. The antioxidant and anti-inflammatory properties of *A. platensis* and *A. maxima* have been shown to reduce tissue damage in rheumatoid arthritis in a rodent model. Therefore, due to the multiple documented health-supportive properties of blue-green algae, they are frequently used as an ingredient in dietary supplements.

A novel *A. platensis*-based aqueous cyanophyta extract (ACE) is a natural extract that promotes anti-inflammatory and pain-relieving activity. The primary component of ACE is phycocyanin, which is known to act as an antioxidant and a selective COX-2 inhibitor with documented anti-inflammatory properties. In addition to phycocyanin, ACE contains anti-inflammatory compounds different from phycocyanin yet with complementary anti-inflammatory properties. The purpose of the two clinical pilot studies reported here was to provide evidence for resolution of chronic pain during consumption of a phycocyanin-enriched extract of *Arthospira*, known to possess synergistic anti-inflammatory effects.

**Materials and methods**

**Consumable nutritional product and placebo**

An ACE derived from *Arthospira* (subspecies *platensis*) was obtained from Cerule LLC, where the extract Cyactiv™ is produced by a proprietary process involving aseptic...
Human clinical pilot studies

Two human clinical pilot studies were conducted on healthy human subjects with well-defined areas of moderate chronic joint pain affecting their activities of daily living. For both studies, 12 study participants were enrolled after obtaining written informed consent, as approved by Sky Lakes Medical Center Institutional Review Board (FWA 2603). Inclusion criteria were subjects of either sex, 45–75 years of age, eating a balanced Western diet, with >6 months of chronic pain in well-defined anatomical area(s) involving joints. Exclusion criteria were recent trauma that would affect pain scoring and joint movement. Subjects were instructed to maintain their consumption of over-the-counter pain medication and supplements constant during the study.

Study design I

The initial study was conducted as an open-label single-arm 4-week study, where 12 subjects (Table 1) consumed 1 g ACE daily for the study duration (Figure 1). Questionnaire-based data collection happened on a weekly basis during visits to NIS Labs. Questionnaires included an activities of daily living questionnaire and pain scores for each person’s primary and secondary area of chronic pain complaint. The pain scores were determined from responses, using visual analog scales, to questions about pain both at rest and when physically active.

Results

All study participants from both Study I and Study II completed study participation and reported good tolerability.

Table 1 Demographics for Study I (open-label 4-week study consuming 1 g ACE daily)

<table>
<thead>
<tr>
<th></th>
<th>Age, years (mean ± SEM)</th>
<th>BMI, kg/m² (baseline)</th>
<th>BMI, kg/m² (4 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>53.1±6.8</td>
<td>31.4±8.5</td>
<td>29.4±7.7*</td>
</tr>
<tr>
<td>Range</td>
<td>40–62</td>
<td>17.65–51.1</td>
<td>17.4–48.1</td>
</tr>
</tbody>
</table>

Note: *The mild reduction in BMI seen over the 4-week period was analyzed using the “within-subject” paired t-test and was highly significant (P<0.01).

Abbreviations: BMI, body mass index; ACE, aqueous cyanophyta extract; SEM, standard error of the mean.

Table 2 Demographics for Study II (placebo-controlled crossover dose study)*

<table>
<thead>
<tr>
<th></th>
<th>Age, years (mean ± SEM)</th>
<th>BMI, kg/m² (baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>58.3±8.2</td>
<td>27.0±5.4</td>
</tr>
<tr>
<td>Range</td>
<td>41–72</td>
<td>17.9–36.3</td>
</tr>
</tbody>
</table>

Note: *The three periods of consumption of either placebo, 250 mg ACE, or 500 mg ACE were 1 week duration, separated by 1 week washout.

Abbreviations: BMI, body mass index; ACE, aqueous cyanophyta extract; SEM, standard error of the mean.
and absence of gastric upset. This was an important observation when consuming a known COX-2 inhibitor, phycocyanin, at a dose up to 300 mg/d (~30% of the 1 g/d dose of ACE).

The initial 4-week study also showed a very mild reduction in body weight as reflected by the body mass index (BMI) (Table 1). People with low BMI at study start showed only minimal change well within the range of normal daily variations, whereas people with higher BMI at study start showed a mild reduction in BMI such that the overall BMI changes in the study population at study end reached a high level of statistical significance when compared to BMI at study start (P<0.01). The subsequent dose study did not monitor weight since the consumption periods were of only 1 week duration and used lower doses of product.

Significant changes in pain scores were seen in the initial 4-week study, during which time the study participants consumed 1 g ACE daily (Figure 3). The baseline pain score for each person’s identified area of primary pain complaint at baseline was similar between pain at rest and pain during physical activity. In contrast, each person’s secondary area of chronic pain was less aggravating as shown by lower score at rest but increased during physical activity. The pain associated with the increased physical activity at baseline and showed rapid reduction, reaching significance (P<0.01) after 1 week of consumption. The pain associated with the secondary pain complaint was lower at rest and higher during physical activity at baseline and showed rapid reduction, reaching significance (P<0.01) after 1 week of consumption. The average pain scores for the secondary pain complaint were reduced to very low levels after 4 weeks, reaching a very high level of significance (P<0.001).

For the primary pain complaint, the pain levels at rest and when physically active were comparable at study start, showed a reduction that became significant after 2 weeks consumption (P<0.01), and then plateaued, likely due to increased physical activity. The pain associated with the secondary pain complaint was lower at rest and higher during physical activity at baseline and showed rapid reduction, reaching significance (P<0.01) after 1 week of consumption. The average pain scores for the secondary pain complaint were reduced to very low levels after 4 weeks, reaching a very high level of significance (P<0.001).

For the subsequent dose study, where each dose of ACE (0 mg, 250 mg, and 500 mg) was consumed for a 1-week duration separated by 1-week washout periods, the rapid improvement in chronic pain of a person’s secondary pain complaint area during physical activity seen in Study I was
confirmed (Figure 4). Data on pain scores were analyzed for those people with pain scores at baseline above 5/100, thus excluding people with no pain during physical activities at the start of each 1-week study interval. The reduced pain after 1-week consumption of both the 500 mg and the 250 mg doses was highly significant when compared to consumption of placebo (\(P<0.01\)).

**Discussion**

The anti-inflammatory effects of crude *Arthospira* products, as well as phycocyanin-enriched extracts, are well documented.\(^8,9,23-25,27-29\) However, to the best of our knowledge, this study is the first to establish an association with consumption of an aqueous *Arthospira* extract enriched in phycocyanin and other aqueous compounds to pain relief in a human population. The overall speed and magnitude of resolution of some aspects of chronic pain suggests an underlying effect on oxidative stress and inflammation. Several parallel mechanisms of antioxidant and anti-inflammatory activity of ACE have shown that the bioactivities of the extract are more complex than what can be accounted for by the content of phycocyanin alone. The findings that ACE contains compounds capable of inhibiting the lipoxygenase inflammatory enzyme,\(^23\) in conjunction with its content of the COX-2 inhibitor phycocyanin, suggest that the rapid effects seen reflect, at least in part, a synergistic effect of inhibition of several inflammatory enzymes.

A complex relationship between reduction of pain scores and increased physical activity is a known factor in studies of relief of chronic pain.\(^3\) The scores for activities of daily living for this study population showed a dose-dependent relationship, with people reporting improved ability to perform daily activities during the week when they were consuming a 500 mg dose of ACE.

The observation that people with a higher BMI at study start showed weight reduction during the 4-week consumption of ACE suggests that previously reported effects of *Arthospira*-based nutritional products on metabolism\(^22\) are at least in part due to aqueous compounds. In light of the known associations between obesity and inflammation,\(^30\) a future study of longer duration is warranted and would monitor weight, body fat percentage, and metabolic hormones, as well as fasting glucose and insulin.

**Conclusion**

In conclusion, the data presented here show rapid effects on the resolution of chronic pain in people consuming ACE, accompanied by increased ability to perform daily activities. The documented effects of ACE on other aspects of inflammation, including inhibition of free radical formation by inflammatory cells,\(^23\) suggest a multifaceted mechanism underlying the clinical observations. Future work is warranted, including a double-blind, randomized, placebo-controlled study on chronic joint-related pain, as well as evaluation of effects on inflammatory and metabolic biomarkers.

**Disclosure**

GSJ, KFB, SGC, and VLA are employees of NIS Labs. JG and AE are employed by Cerule LLC, the sponsor of this study. The authors report no other conflicts of interest in this work.
References


26. Notice to US Food and Drug Administration that the use of CyaninPlus is Generally Recognized as Safe. Filed March 2012; GRAS Notice 424; Date of Closure December 6, 2012.


